TO WHAT EXTENT DOES PHARMACEUTICAL COMPANY RESEARCH IN SOUTH AFRICA REFLECT THE COUNTRY'S BURDEN OF DISEASE?

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Declaration

I, Jeanne Hoerter, declare that this research report is my own work. It is being submitted for the degree of Master of Public Health in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Abstract

This study compares pharmaceutical company research on new medicines in South Africa with the country's burden of disease and describes the process and criteria that companies use to set their research priorities. A quantitative survey of pharmaceutical companies shows that company research conducted from 2000 to 2003 is moderately associated with the country's burden of disease estimates for 2000. The degree of association is dependent on which measures of company research and burden of disease are compared, and which comparative statistic is used. A qualitative analysis of company interviews reveals that feasibility of clinical trials, market forces, and environmental factors are core criteria for company research priority setting. The burden of disease, although important, is not a sole criterion, and has considerable limitations. Furthermore, this study reveals the complex nature of health priority setting by pharmaceutical companies and thus can assist policy decision makers in identifying practical strategies to encourage research in diseases of need by pharmaceutical companies.

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Definitions

Burden of Disease (BoD) – A "comprehensive measure of the health status of the nation by assessing ill health and causes of death [and] includes fatal and non-fatal outcomes" (MRC 2003a, 1).

Clinical Trial – "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" (DoH 2000, 71).

Contract Research Organisation (CRO) – "A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions" (DoH 2000, 71).

Disability Adjusted Life Year (DALYs) – "A single measure of burden of disease, using time to equate death and disability, it comprises of years of life lost (YLLs) due to premature mortality and 'years lived with a disability' (YLDs), weighted according to severity of disability. It is thus a summary measure of population health, combining information on death and non-fatal health outcomes. It effectively measures the future stream of health years of life lost due to each incident case of disease or injury" (Bradshaw, et al., 2003b, 1).

Investigational Product – "A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (DoH 2000, 73).

Investigator – "A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator" (DoH 2000, 73).

Participants – people who participate in either the control or intervention arm of a clinical trial

Phase I – A "new drug, vaccine or medical device[*] is tested in a small group of usually healthy persons for the very first time…to determine the general safety, the correct dosage and possible negative or undesirable effects" (DoH 2002, 2).

[*] Although the DoH definitions regarding clinical trials include medical devices, MEDICAL DEVICES ARE NOT INCLUDED in this study

Phase II – “The new drug, vaccine or medical device is tested in a larger group (several hundred healthy people)…[and possibly] people with the disease being tested for…to further test the safety and effectiveness of the new drug, vaccine or medical device” (DoH 2002, 2).

Phase III – “The new drug, vaccine or medical device is tested in a larger group (several hundred to a few thousand) of people who suffer from the disease/illness for which the new drug, vaccine or medical device is intended [to evaluate] the effectiveness and possible undesirable effects [and compare it] to old registered (licensed) drugs, vaccines or medical devices, or alternative treatment options” (DoH 2002, 3).

Phase IV – “Trials after the new drug, vaccine or medical device has been registered and licensed for sale by the Medicines Control Council (MCC)…the drug, vaccine or medical device is tested in several thousand people to:

- define its safety, effectiveness, long-term undesirable effects,
- test the new drug, vaccine or medical device in certain high risk sectors of the population like children, the elderly, people with liver and kidney disease, and
- find new uses (indications) of the new drug, vaccine or medical device” (DoH 2002, 3).

Pre-Clinical Research – The study of new medicines or devices “over a long period, in the laboratory and in various animals to establish its initial safety and effectiveness” prior to testing or trials in people (DoH 2002, 2).

Site - The location(s) of a clinical trial which is managed by a principal investigator

Years Life Lost (YLL) – “calculated by subtracting a person’s age at death from his or her life expectancy in the absence of a given disease” (Gross, et al., 1999, 1882)

1.0 Introduction

This study compares pharmaceutical company research on new medicines in South Africa with the country's burden of disease and describes the process and criteria that companies use to set their research priorities.

1.1 Summary of Problem

It is unknown to what extent pharmaceutical company research in South Africa reflects the country's burden of disease (hereinafter referred to as BoD), or how companies set their research priorities. This is important to examine from a public health perspective because if private pharmaceutical industry research efforts in the country are to be leveraged to meet public health needs, policy makers need to first establish a baseline relationship between company research and the country's health needs in order to identify opportunities for research. First, the use of BoD as a measure of a country's health need is a common starting point for health priority setting, with the assumption that there should be some alignment between priorities and needs. This assumption underpins growing concerns from public health experts that pharmaceutical companies do not conduct research in diseases with high burdens in low- and medium-income countries. However, the limits on the use of BoD as a means of quantifying health need and as a sole comparator for research are recognised in this report.

Second, although comparing research with BoD is a first step toward identifying opportunities for research, the process of health research priority setting is far more complex. Therefore, policy makers need to understand how companies set their research priorities so that practical policies to support research in diseases of need can be developed. The specific processes and criteria companies use to set research priorities in South Africa has not been thoroughly studied. It is important to note that South Africans also benefit from other global research conducted outside of the country, which was not captured in this study due to the difficulties in obtaining disease-specific

international research data. However, this study can provide an initial platform for public and private industry policy makers to maximise private pharmaceutical industry research in South Africa to benefit public health needs.

1.2 Overall Aims of the Study

The aims of this study were to:

- Identify the disease priorities for pharmaceutical company clinical research in South Africa from 2000 to 2003, inclusive, through a cross-sectional quantitative survey of pharmaceutical companies in the country.
- Compare the company disease priorities with the Medical Research Council's South African National BoD Estimates for 2000 (Deaths, Years Life Lost (YLLs) and Disability Adjusted Life Years (DALYs)) in order to identify areas of alignment and gaps *(Definitions)*.
- Examine the processes and criteria pharmaceutical companies use to decide upon research priorities in the country via a qualitative analysis of interviews from purposively selected companies.

1.3 The Importance of Investigating Health Research Priority Setting

Bradshaw et al argued, "In the health sector scarcity of resources makes priority setting imperative" (Bradshaw et al 2003b, 1). This sentiment was a predominant theme in the literature. In 2001, the South African Department of Health released a 'Health Research Policy in South Africa' which stated that, "Due to the transformation of the health care delivery system and the need to address the pressing health and development challenges in the country, it is imperative that health research priorities be determined for South Africa in both the short and long term" (DoH 2001, 2). The South African National Health Act created a National Health Research Committee to identify and coordinate public health research priorities (Republic of South Africa 2002; COHRED 2001). At the international level, the World Health Organisation Advisory Committee on

Health Research created a handbook on health research priority setting which stressed that "Resources are finite…different options need to be weighted before resources are allocated and a course of action decided. The overall goal is to allocate resources more effectively" (WHO 2001, 2).

Much of the literature on the importance of health priority setting comes from the public sector point of view – how to allocate national resources to improve a country's population health. There were few studies on health research priority setting from the private sector perspective – how to provide health care to a consumer market within a company's limited resources. However, some studies combined perspectives and discussed the importance of leveraging private pharmaceutical company research to focus on diseases of public need because of the unique nature of the industry in that it operates according to private market principles yet its research efforts can impact public health (Comanor 1996; Michaud and Murray 1996; Trouiller, Torreele, Olliaro et al 2001; Webber 2003).

1.4 Comparison of Health and Pharmaceutical Research in Relation to Burden of Disease

There has been an increasing interest at global and country levels in comparing public and private research with the BoD as a mechanism for priority setting. The assumption for this comparison is that research should be aligned with burden of disease based on the principle that limited resources ought to be allocated to the greatest needs. For example, in the forward to South Africa's first burden of disease study, William Pick stated, "Country-specific estimates of the burden of disease are crucial for targeting health interventions that make a significant impact on the well-being of the population" (Bradshaw et al 2003a). In reference to new vaccine development and use, Levine and Levine found that, "disease burden seems like an obvious quantitative measure for setting priorities" (1997, 1386). Several studies compared BoD with research such as

the Global Forum for Health Research's work that coined the term "10/90 gap" that arose from its estimates that 10% of the more than US$70 billion spent worldwide on health research and development by the public and private sectors is used for research into 90% of the world's health problems (Global Forum for Health Research 2002, xv). Canada, Australia and the United States have examined their national research funding in relation to their country's BoD (Lamarre-Cliché, Castilloux, LeLorier 2001; Aoun, Pennebaker, Pascal 2004; Gross, Anderson, Powe 1999). In South Africa, one study compared the percentage of conference presentations dedicated to mental health issues with mental health priorities (Flisher, Parry, Stein 2000) and another study calculated ratios of the amount of published randomised clinical research in sub-Saharan Africa with the respective BoD (Isaakidis, Swingler, Pienaar et al 2002).

With specific regard to pharmaceutical industry research, several reports showed that few companies research, develop and launch drugs for neglected diseases (Comanor 1996; Michaud and Murray 1996; MSF/DND Working Group 2002; Yamey 2002). Isaakidis et al argued that companies are reluctant to conduct research in diseases that affect few people, or the poor populations of developing countries (Isaakidis et al 2002). Resnik explained that this "can leave large gaps in our medical knowledge and may fail to promote the interests of all people in society" (Resnik 2003, 1). However, the major challenge with examining the private pharmaceutical industry was the lack of data. Michaud and Murray found that only three companies at the international head office level returned their questionnaire and, "The paucity and lack of comparability of available disaggregated data did not allow us to assess the level of funding allocated to specific health problems with a sufficient level of confidence" (1996, 217). Therefore, although it was recognised that South Africans also benefit from research conducted outside of the country, the difficulties in obtaining international clinical trial level data informed the design of this study such that it focused only on research conducted in South Africa.

No studies in South Africa were identified which quantified pharmaceutical company research according to disease category. The only studies found were general estimates of pharmaceutical expenditure on research (PMA 1997; Wits Health Consortium 2000; Department of Science and Technology 2003). Nor were any studies found which compared pharmaceutical company research to the country's disease burden. Perhaps this is because the country's first ever BoD estimates were only reported by the Medical Research Council (MRC) relatively recently in March 2003. The MRC report "displays the quadruple burden of disease experienced in SA: a combination of pre-transitional diseases and conditions related to under-development and poverty, the emerging chronic diseases associated with affluence, a high injury burden and the extensive HIV/AIDS epidemic" (MRC 2003a, 5). These findings supported the growing significance of non-communicable diseases which was recognised in the WHO Global Burden of Disease report for the sub-Saharan region (Murray and Lopez 1996) and ran counter to the "conventional wisdom that non-communicable diseases are not a high priority area for health research and development in the countries of sub-Saharan Africa" (Unwin, Setel, Rashid et al 2001, 947). Therefore, it was apparent that South Africa's unique BoD profile reflecting challenges of both the developed and developing world was important to consider in this study.

1.5 Understanding How Priorities are Set

The literature investigating how priorities are generally set focused first on the objective trying to be achieved. It was a common approach to analyse alternative priorities in terms of their ability to impact an objective, yet as the International Service for Agricultural Research discovered, "the evaluation does not yet result in clear priorities since several objectives are usually involved [and] priority setting includes the determination of the relative importance of these objectives" (ISNAR 2002, 1).

With regard to health research priority setting, the co-existence of multiple objectives across stakeholders was readily apparent in the literature. The South African

Department of Health's objective was to "improve human health and well-being" (DoH 2001, 2). Resnik suggested that companies' objectives were to make a profit and priorities were based on "market potential, liability costs, the scope of intellectual property protection, market lead time, the expected time from the laboratory to the market, and other factors that affect the profitability of a research investment" (Resnik 2003, 1). In an Australian study on stakeholder priorities for mental health, "different groups of stakeholders tended to have differing perspectives on research priorities, with some major differences between committees that evaluate research grants and consumer and carer groups" (Griffiths, Jorm, Christensen et al 2002, 327). This illustrates that governments, private sector and patients can all have different objectives and that it is critical to clarify whose objective is trying to be met when understanding how health priorities are set.

Recognition of multiple objectives is particularly relevant to this study because much of the concern in the literature that pharmaceutical research does not reflect a country's BoD arises when public sector objectives of reducing a population's overall BoD may clash with private sector objectives of providing medicines to a consumer market. Therefore, how to stimulate private research in the areas of public need was heatedly debated in several articles. It appeared that the differences in objectives was not recognised nor the constraints of the respective parties understood. For instance, arguments that companies have an inherent social responsibility to the developing world; did not recognise that there are other "economic, social, legal, political and obligations and commitments companies face" (Resnik 2001, 11). Resnik further suggested that, "developing countries can work toward attracting research and investment rather than just expect it. For example, they can adhere to intellectual property treaties, insure companies have a good business environment by promoting rule of law, ethical business practices, stable currencies, reliable banking systems, free and open markets, and democracy" (Resnik 2001, 11). However, on the other side, arguments that countries

should create an inviting atmosphere for pharmaceutical companies to conduct research did not recognise that countries often did not have the scientific capacity, had negative experiences with clinical trials in the past, or could not afford to pay international market prices for new medicines (Shah 2003). For those articles that did incorporate the market dynamics of the pharmaceutical industry, the focus was on how to change the current market such that private company objectives could be met and public health needs would not be neglected (Trouiller et al 2001).

Numerous articles devised frameworks for setting health research priorities and each incorporated some measure of BoD. However, most frameworks also stressed the importance of other parameters such as risk factors for disease, current state of knowledge, availability of data, feasibility and cost-effectiveness, potential impact of an intervention, geographic distribution, human and financial resources, ethical and equity issues, and the role of actors and processes involved in decision-making. Other frameworks took these factors one step further and examined priority setting at the individual, local, national, regional and global levels (Levine and Levine 1997; COHRED 2001; Schneider 2001; Global Forum for Health Research 2002; Republic of South Africa 2002; WHO 2001; Francisco 2004). Shortcomings of these paradigms were also debated and Fraser identified core problems where, i) there is little known about the health problem, ii) current control methods are unsustainable, iii) there are complex risk factors, and iv) the disease burden and resources for control vary greatly from one place to another (Fraser 2000, 1054).

With regard to the private pharmaceutical industry specifically, additional considerations were raised, such as:

- External factors - macroeconomic stability, tax incentives, trade policies, judicial systems, regulation, intellectual property rights, human resources, public research, education system, natural resources and information networks
- Market factors - overall market size, the public perception of risk associated with the disease, government and private purchasing, pricing, product liability, competitors, and anticipated return on investment
- Internal factors - technological feasibility and cost of development and production, probability of success and expertise of the company (both in research & development and marketing). (Dupuy and Freidel 1990; Levine and Levine 1997; CMCS 2001; Trouiller et al 2001; Andre 2002; Webber 2003).

There was little agreement in the literature on how to set public or private health research priorities, but all did include some form of burden of disease measure as a criterion. The authors did concur that the process is complex and the inclusion of multiple parameters was essential.

1.6 Methods for Health Priority Setting Studies

In light of the multi-faceted nature of priority setting, specific concerns were raised with regard to comparing research solely to BoD as a method for priority setting. Harold Varmus, M.D., USA, and Head of the National Institutes of Health (NIH) in 1999, felt that "it is important to emphasize that there is not – and should not be – an absolute correspondence" [between NIH funding and the BoD] because of the inherent methodological difficulties and the importance of other factors in priority setting" (Varmus 1999, 1914). Moreover, "assessing research according to money spent on a specific disease is imprecise" (US Dept of Health and Human Services 2004, 2) and the "serendipitous nature of science must be considered; investigations in one area frequently yield fruitful results in another…Hence, it may be overly simplistic to link

funding to specific diseases. However, awareness of this factor does not preclude the need for rational methods to assign priorities…" (Gross et al 1999, 1886).

Varmus further argued that policy makers should not just focus on current burdens of disease, but they need to consider "projections of future patterns of disease and the effects of demographic changes (such as aging) and personal habits (such as tobacco use)…" (Varmus 1999, 1914). Others suggested that "disease focus is only one dimension of health research and…major risk factors affecting health also have to be prioritised" (Global Forum for Health Research 2003, 1). The World Health Report 2002 reflected this concern by identifying 10 risk factors that account for more than a third of worldwide deaths (WHO 2002), and the MRC's BoD report also drew attention to the importance of risk-prevention strategies (Bradshaw et al 2003a, xi).

Furthermore, the literature revealed that BoD calculations are evolving and are not yet 100% accurate for use as a method for priority setting. Traditionally, mortality data was used as a BoD indicator; however, new measures that incorporate premature mortality and morbidity now provide a more comprehensive picture of the BoD. Such measures are: Years Life Lost (YLLs), "calculated by subtracting a person's age at death from his or her life expectancy in the absence of a given disease" (Gross et al 1999, 1882); and Disability Adjusted Life Years (DALYs), "calculated by estimating Years Life Lost (YLL) and Years Lived with Disability of known severity and duration (YLD) and then adding them." One DALY is one lost year of healthy life (Murray and Lopez 1996, 7).

However, two main concerns emerged from the literature with regard to the calculation of BoD measures: 1) technical issues, and 2) the social values incorporated into the measures (Gross et al 1999, 1885). Technical issues stem from the lack of quality data. There is often no central repository of data, reporting errors and improper coding are common, composite measures are difficult to break down, proxy measures are

imprecise, and some diseases impact morbidity of other diseases - all which impact the validity of BoD measures (Gross et al 1999; Morrow and Bryant 1995; Murray and Lopez 1996; Schneider 2001). Social values incorporated into BoD measures also result in variability because not all people agree on what is ideal life expectancy, how valuable is healthy life in young adulthood versus older age, which disability is more severe than another, or is living with a disability better than premature death? In addition, other personal judgments such as the value of incremental improvements in health, co-morbidity, gender, equity, poverty, cost-effectiveness and avoidability add to the inconsistency of BoD calculations (Bradshaw et al 2003a; Gross et al 1999).

Therefore, although the literature supported the use of BoD as a criterion in the design of priority setting frameworks, it suggested that it should not be the sole criterion for comparing research with health needs and was clear on its limitations (Morrow and Bryant 1995; Murray and Lopez 1996; Schneider 2001).

Lastly, a variety of comparative methodologies were used in general health priority setting studies identified in the literature. Studies evaluated multiple BoD measures that included incidence, prevalence, hospital days, death, YLLs and DALYs. Furthermore, different indicators of research were assessed such as expenditure on trials and number of publications. For studies that compared multiple measures, all concluded that the results were highly dependent on which measure was used (Aoun et al 2004; Gold and Muennig 2002; Gross et al 1999). Statistical techniques used included percentage comparisons, ratios, correlation coefficients, and regression analyses, and the studies' results also depended on which statistic was used (Aoun et al 2004; Gross et al 1999; Jorm et al 2002; Lamarre-Cliché et al 2001; Swingler et al 2003). Therefore, authors cautioned that "policy makers could be misled by using a single burden of disease [measure]", or measure of research, or comparative statistic because "advocates interested in promoting research on particular diseases could select measures that best

support their cause" (Gross et al 1999, 1885-6). It was apparent that there is no well-established methodology for health priority setting studies in general and that interpretation of any such study should be made clearly within the context of its study design.

1.7 Implications of the Literature Review

The literature revealed that the aims of this study to identify pharmaceutical company research priorities in South Africa and compare them with the country's BoD were important because there is little data on health research priority setting from the private pharmaceutical sector perspective. A better understanding of how pharmaceutical companies prioritise their disease research in the country would enhance public and private decision-maker's ability to devise practical policies to support company research in diseases of need.

In summary, key issues raised in the literature that are important to this study are: 1) the importance of various stakeholder objectives, 2) the multi-faceted nature of health research priority setting, 3) the limitations of relying solely on BoD as a comparative indicator for health need, and 4) the need to compare multiple measures of research and BoD with a variety of statistical tools in order to have a more complete picture of their relationship. Furthermore, although it was recognised that South Africans also benefit from research conducted outside their country, the same difficulties in obtaining disease-specific research data from companies' global offices by other researchers was anticipated with this study, which resulted in limiting its scope to research in South Africa. These key issues greatly informed the design and interpretation of this study, and pending the development of other comparators and methodologies, the results of this study remain instructive since no such baseline has ever been established.

2.0 Methods

The study design, sampling method, sample size and characteristics, processes used for data collection and measurement, ethical and confidentiality considerations, and data analysis are addressed below. These are followed by limitations of the study design.

2.1 Two-Part Study Design

Part One of this study was cross-sectional and descriptive. It compared quantitative data collected through questionnaires completed by participating pharmaceutical companies in South Africa with the South African Medical Research Council's BoD estimates for 2000, which included Deaths, Years Life Lost (YLLs) and Disability Adjusted Life Years (DALYs).

Part Two of this study was exploratory and involved thematic analyses of qualitative data collected through semi-structured interviews with Medical Directors from purposively selected pharmaceutical companies.

2.2 Study Population

The source for the study population comprising all pharmaceutical companies in South Africa was the 2003 South African MIMS Desk Reference (compendium of manufacturers and medicines) that listed 79 pharmaceutical companies operating in the country (MIMS 2003). It was the most comprehensive list of companies publicly available.

Inclusion criteria were:

- Pharmaceutical companies registered in South Africa. *Rationale: Only companies with products available in South Africa could potentially meet the country's BoD. Furthermore, it was impractical to assess global research due to the lack of available data.*

- Clinical trials that received approval by an accredited South African Ethics Committee. *Rationale: Only those trials approved by an accredited South African Ethics Committee were appropriate to consider and obtaining ethics approval demonstrated a company's intent to conduct research in a particular disease category.*
- Clinical trials that received ethics approval during the period from 1 January 2000 to 1 January 2004. *Rationale: Four years provided a sufficient range of data, and trials before 2000 were excluded because the data was difficult to obtain due to numerous pharmaceutical company mergers.*
- Clinical trials for an investigational product without a generic equivalent available on the South African market at the time of Ethics Committee approval. *Rationale: Research aimed at identifying new medicine to address unmet medical needs was the focus of this study.*
- Multiple trials relating to the same investigational product. *Rationale: It is possible to have multiple trials researching a new indication, strength, dosage, or drug delivery system for the same product. Each trial was indicative of research in specific disease category.*
- Clinical trials that were either conducted in full by a pharmaceutical company or out-sourced to a Contract Research Organisation (CRO). *Rationale: Small and large companies alike often do not have capacity to manage their own research so trials were sometimes contracted out, but with local company oversight.*

Exclusion criteria were:

- Clinical trials on generic equivalents, such as bioequivalence or pharmacovigilence studies. *Rationale: Research on existing molecules does not address the need for new medicines for unmet medical needs.*

- Clinical trials on medical devices or diagnostic equipment not specifically related to an investigational product (e.g., stents, pacemakers, dialysis supplies). *Rationale: The scope of this study was medicine only.*
- Clinical trials conducted by Contract Research Organisations (CROs) for parent companies outside of South Africa without the knowledge of local affiliate. *Rationale: This rarely happens nowadays, and this data was not feasible to obtain.*
- Clinical trials conducted by Contract Research Organisations (CROs) for companies not registered in South Africa. *Rationale: Only companies that are registered in South Africa were included.*
- NGOs and government research. *Rationale: This study focused only on the pharmaceutical industry.*

In summary, the inclusion and exclusion criteria limited the study population to pharmaceutical companies registered in South Africa that were conducting clinical trials approved by an accredited ethics committee for new medicines.

2.3 Sampling Method

Data on pharmaceutical company clinical trials was not available through either the Medicines Control Council (MCC) or the more than 20 Ethics Committees. Computerised records were not often kept, disease categories were not consistently captured, and most importantly, confidentiality of each company's data needed to be maintained by the respective custodian of information (MCC 2003a, 2003b; SAAPP 2003). Therefore, data for this study had to be obtained directly from each company.

Sampling method – Part One

All of the 79 companies listed in the 2003 MIMS Desk Reference were considered. To ensure completeness, the MIMS list was cross-referenced with member lists from physician, pharmacist, and pharmaceutical company trade associations involved in

clinical trials and no gaps were found (SAAPP 2003; Wits Health Consortium 2000; IMSA 2003; PMA 2003)

Each company was then contacted via phone or email to determine if they met the inclusion criteria. 24 companies met the inclusion criteria and follow up meetings were held with each of their Medical Directors to assess their willingness to participate. 18 companies agreed to participate, and 17 companies actually completed the questionnaire that resulted in a 70.86% response rate for Part One (17 out of 24 companies). The 24 eligible companies represented more than 61% of private pharmaceutical market sales, and the remaining 39% of the private market was from non-eligible companies. The 17 participating companies represented more than 44% of the private market (IMS 2003). Public market figures were unavailable. The 17 participating companies represented a good range of sales, clinical research staff, disease priorities, headquarters location and number and types of trials. Therefore, although the sample was non-random, it was a substantial portion of the study population. It was inappropriate to select a smaller sample size since it was feasible to include all 24 eligible companies, and 17 participating companies was sufficient for the descriptive purposes of this study. The characteristics of the 7 non-participating companies did not differ greatly from the participating companies. Given the confidential nature of this study and the small sample size, further exploration into non-responders was not conducted so as to preserve the confidentiality of the participants and non-participants.

Sampling method – Part Two

After completion of the questionnaires, three (3) Medical Directors from companies with the lowest number of trials and three (3) Medical Directors from companies with the highest number of trials were selected for interviews. One of the companies with a low number of trials was unavailable for an interview and was replaced with another

company with an average number of trials. A larger sample for interviews was not chosen because the goal was not statistical inference, but rather to explore qualitatively how companies prioritise disease categories for research. Although purposive sampling did not enable precise generalisations about the study population, a sufficient range of company sizes and disease priorities were represented which was important so that the results would enable any potential differences due to company size or disease focus to emerge.

2.4 Data Collection and Measurement

In order to improve the quality of both the questionnaire and interview response rates, pre-meetings were held with members of the Pharmaceutical Manufacturers Association (PMA), Innovative Medicines South Africa (IMSA) and the South African Association of Pharmaceutical Physicians (SAAPP) in order to generate interest in participation. The questionnaire and interview questions were piloted with 3 Medical Directors to check for understanding, fine-tune questions, assess feasibility and time required to obtain data. These 3 Medical Directors were from companies that were part of the final sample. However, since the questionnaire did not change significantly between the Medical Director's preview and the final version, their familiarity with the questionnaire did not negatively impact the study, and perhaps improved their ability to fill it out correctly.

Data collection and measurement – Part One

The questionnaire in Part One of the study had two-parts. Part I of the questionnaire asked contextual questions in order to characterise the scope of the company's research in South Africa, which included what the company's top 5 disease priorities were (referred to as *company priority* in the results). This study did not seek to quantify expenditure due to the challenge of accessing verifiable financial data. Part II of the questionnaire asked specific questions relating to each clinical trial, which included what was the trial's disease target (referred to as *trial priority* in the results), phase, number of

planned and final participants, and number of planned and final sites *(Appendix 1 – Company Questionnaire)*. The questionnaire was distributed and returned electronically within 1 to 14 weeks after regular phone calls and emails to kindly remind participants. Companies self-reported results, and I entered the data into a Microsoft Excel® spreadsheet (Microsoft 2000). I then verified the data by double-checking the questionnaires with the Excel® spreadsheet twice and any anomalies were confirmed with the respective company.

In order to achieve a true comparison of disease categories between pharmaceutical company research and the MRC's BoD study, permission was received from Debbie Bradshaw at the South African Medical Research Council to use the same disease codes for this study as those that the MRC devised for their National Burden of Disease study (Bradshaw 2003). However, not all of the 24 MRC disease categories were amenable to pharmaceutical intervention (e.g., cot death) and it would have been inappropriate to compare pharmaceutical clinical research with such disease categories. Therefore, 3 medical doctors, who were not participants in the study, were consulted to advise on which disease categories of the MRC's BoD study should be excluded for this reason. The doctors identified: nutritional deficiencies, congenital abnormalities, cot death, unintentional injuries and intentional injuries. These 5 disease categories were then excluded, and the remaining 19 MRC disease categories were used for this study's comparative calculations. A 20th category "Other" was added to capture those conditions or disorders which the MRC had not included in their taxonomy (e.g., pain, smoking addiction) and were reported descriptively *(Appendix 3 - Disease Categories and Codes).*

Data collection and measurement – Part Two

The exploratory interviews in Part Two of the study were based on three open questions which identified the process and timing for *how* the company decides to conduct clinical

trials in South Africa, *what* issues or factors the company considers when deciding to conduct a trial, and *why* the company prioritises disease categories for research in South Africa in the way that they have *(Appendix 2 – Pharmaceutical Company Semi-Structured Interview Questions)*.

The questions were asked during telephone interviews with Medical Directors, given difficulties of arranging face-to-face interviews. The interviews were not recorded, but diligent notes were taken and at the end, a summary of the response was recited back to the participant to ensure accuracy. The accuracy of my summary feed-back was commended by all 6 interviewees. The interview data were then transcribed by me into an Excel® spreadsheet for further analysis. Statements by interviewees were coded according to common themes that emerged from them, and the data was then tabulated by code across interviews to allow similarities and differences between the interviews to be identified.

2.5 Data Analysis

Quantitative Analysis – Part One

First, summary descriptive statistics were calculated in Excel® for each measure of company research per disease category:

1) total number of diseases reported as one of the top 5 company priorities *(company priority)*;
2) total number of diseases reported as a trial priority *(trial priority)*;
3) total number of participants planned *(participants planned)*;
4) total number of participants enrolled* (*participants enrolled)*;
5) total number of sites planned *(sites planned)*; and,
6) total number of final sites *(sites final).*

* participants 'enrolled' means the participants signed informed consent

The measures of company research by disease category were not weighted (i.e., 10 trials equalled 10 participants planned for cardiovascular disease). It would have been an imprecise exercise to rationalise why one measure of company research should be weighted more than another (i.e., why trials may be more important than participants

planned). Moreover, no other previous comparative BoD study identified in the literature review weighted measures of research.

Second, any data outliers (extreme values or omissions) were verified with the respective company. Sub-analysis summarised the number of clinical staff, phases of trials, prevention and/or treatment trials, multi-country trials, registration status of the product, and trials contracted out.

Third, comparative statistical analysis was performed between the measures of company research and the MRC BoD measures (Deaths, YLLs, DALYs). Multiple measures of BoD were used as comparators to address one of the key methodological issues revealed in the literature review, namely the variability of results depending on which BoD was used as a comparator. Furthermore, Debbie Bradshaw suggested that the quality of the DALYs in the MRC report were not as robust as the Death and YLL data (Bradshaw 2004). Therefore, this study examined all three MRC BoD comparators: Death, YLLs and DALYs.

The use of multiple comparative statistical analyses using rankings (Spearman's rank coefficient of correlation) and actual values (Pearson's coefficient of correlation and Regressions) was an integral part of this study's design so that any potential variations in the results due to the use of different statistical tools could emerge. This was an intentional effort to address another methodological issue that was identified in the literature review, namely that results of other comparative BoD studies differed depending on which statistical tool was used.

For the comparative statistics, all data were transformed by taking the logarithm*. This was important to do because the wide range of actual values (0 - 5 067 490) was too broad to see any patterns. Other comparative BoD studies identified in the literature review also logged their data (Gross et al 1999), and because for regressions "suitable transformations of data can sometimes be found that will permit a nonlinear model to be approximated by a linear one (Weisberg 1985, 141)," it was decided that logging the data would provide the best format for analysis.

Non-parametric statistical analysis using Spearman's rank coefficient of correlation was conducted to determine the relationship between the relative rankings of the measures of research and the MRC's BoD measures (logging had no impact on ranks). Then, parametric statistics using Pearson's coefficient of correlation were calculated to determine the relationship between the actual values (logged) of the respective measures. Both Spearman's rank and Pearson's correlations were then conducted again excluding HIV/AIDS given the high value of HIV/AIDS in all BoD measures. The criterion for significance was $p < 0,05$ for a two-tailed test.

The Spearman's rank and Pearson's correlation coefficients only summarised the data in a single number and did not clearly identify alignment and gaps for specific diseases with the BoD measures. Therefore, it was essential to perform regression analysis with the actual logged values (not the ranks) and then plot the regressions to better illustrate and adequately differentiate which diseases were in alignment and which were not. For this reason, those regressions with **both** a Spearman's and Pearson's statistical significance of $< 0,05$ were plotted to visualise gaps and alignment for specific disease categories. (The remaining regressions were also plotted but there was too much variability to draw conclusions).

* Because there were 0 Deaths and YLLs for the Sense Organs and Oral Conditions disease categories, in order to log transform the data, dummy figures of 2 Deaths and 2 YLLs for sense organs and 1 Death and 1 YLLs for oral conditions were added upon advice from the MRC. These low substitute numbers did not impact the results, but did allow the data to be logged. Lastly, all data was logged at "x + 1" due to a few variables with 0 observations.

This resulted in Spearman, Pearson and regression calculations using Stata® Statistical Software (Stata 2003) for all 19 MRC disease categories for the following measures*:

- Companies vs. Deaths
- Companies vs. YLLs
- Companies vs. DALYs

- Trials vs. Deaths
- Trials vs. YLLs
- Trials vs. DALYs

- Participants planned vs. Deaths
- Participants planned vs. YLLs
- Participants planned vs. DALYs

- Participants enrolled vs. Deaths
- Participants enrolled vs. YLLs
- Participants enrolled vs. DALYs

- Sites planned vs. Deaths
- Sites planned vs. YLLs
- Sites planned vs. DALYs

- Sites final vs. Deaths
- Sites final vs. YLLs
- Sites final vs. DALYs

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* Predictive variables (X)

- MRC's 2000 South African burden of disease estimates for Death, Years Life Lost (YLLs) and Disability Adjusted Life Years (DALYs)

(Table 2: MRC Burden of Disease Estimates, 2000)

and;

Dependent variables (Y)

- Number of company priorities, trial priorities, participants planned and enrolled, sites planned and final

(Table 1: Company, trial and participants planned disease priority numbers and rankings, and; Appendix 5: Participants enrolled, sites planned, and sites final disease priority numbers and rankings).

Qualitative Analysis – Part Two

First, interview responses that were in common or unique were identified, counted and coded into categories. Sub-codes were allocated to further differentiate within categories. Second, similarities and differences across interviews were examined to identify any relationship between the size of the company and/or its disease specialties and the responses. Third, the broad themes were compared with the quantitative responses from the questionnaire, opinions found in the literature review, and my own expectations that were formed as a result of my initial consultations with industry and public health experts while piloting the questionnaire. For example, the high amount of research for cardiovascular disease found in the questionnaire was evaluated within the context of the multi-faceted nature of priority setting and the limitations of relying solely on BoD that were revealed in the literature review, along with my expectations that companies may rely on more than BoD criteria to prioritise their research as was mentioned to me in preliminary discussions. This process enabled me to systematically interpret the qualitative interview findings and explain the results of the quantitative questionnaire (i.e., what company disease priorities are and how and why companies may choose them).

2.6 Ethical and Confidentiality Considerations

Approval of the study protocol by the University of the Witwatersrand Faculty of Health Sciences was received on 4 December 2003, protocol # M03-09-16. Ethics clearance was received by the University of the Witwatersrand Committee for Research on Human Subjects (Medical) on 3 September 2003. Furthermore, informed consent for both the questionnaire and in-depth interview was signed by each participant, and confidentiality agreements were signed between each participant and myself to protect company- and individual-specific data. Also, although my advisor and statistician did not receive any company- or individual-specific data, confidentiality agreements were signed with each of them to protect aggregate industry data. There were no financial or non-financial

incentives for participants, and I had no affiliation or support from any company or industry association. Non-responders and responders were not identified nor described in order to preserve their confidentiality.

2.7 Limitations

There were some potential limitations in the study design regarding selection, measurement and other biases, however, all reasonable effort was undertaken to minimise them.

Selection bias

Selection-bias could have been introduced given that only those companies willing and able to provide data participated. Furthermore, those companies that expected their research to be line with the BoD may have been more willing to participate which could have biased results to be more in line with BoD, and those companies that expected to be out of line may have opted not to participate. However, selection bias was considered minimal because the final response rate was 70,86% (17 out of 24 eligible companies participated) and the data represented a good range of sales, clinical research staff, disease priorities, headquarters location and number and types of trials. Non-response was minimised through numerous pre-meetings with all eligible companies, industry associations, and follow-up phone calls to encourage participation. Also, assurances of confidentiality were formalised through informed consent and confidentiality agreements with each participating company. However, due to the confidential nature of the study design, characteristics of non-responders were not reported so it is unknown how many trials out of the potential total are missing, but it is considered to be minimal.

Measurement bias

A major advantage of this study was that the companies directly provided the information so there was little room for third party mistakes. However, a potential disadvantage was that measurement bias could have been introduced because the data was not verifiable through other sources due to the confidential nature of the study. Companies may have inaccurately reported either unintentionally by misinterpreting the question or definitions, or through questionnaire fatigue; or intentionally, by reporting only those trials that favourably reflect the BoD. Unintentional mistakes were minimised by piloting the questionnaire to improve its precision, being available throughout the process to answer any questions, and verifying any identified anomalies. Intentional mistakes were considered minimal because this study's company reported disease priorities did reflect the areas of expertise mentioned in the company annual reports and/or the company's current product range. Furthermore, the interviews were completely voluntary and confidentiality was maintained so there was no reason to believe that the answers did not reflect the opinion of the interviewee.

Other biases

Investigator bias could have been introduced during the data collection, analysis or interpretation because of my previous 9 years of experience in the pharmaceutical industry. My experience was actually an advantage because it assisted me in gaining access to the companies. Furthermore, this research topic was completely my own idea and neither my previous employers nor any other pharmaceutical company or association was affiliated with or funded the study. Potential bias was minimised by adhering to conventional statistical methods for the calculations and using accepted qualitative techniques such as such as comparing and contrasting findings amongst the interviews and external sources *(Data Analysis).* In addition, two independent researchers, my advisor and statistician, reviewed my practices.

3.0 Results

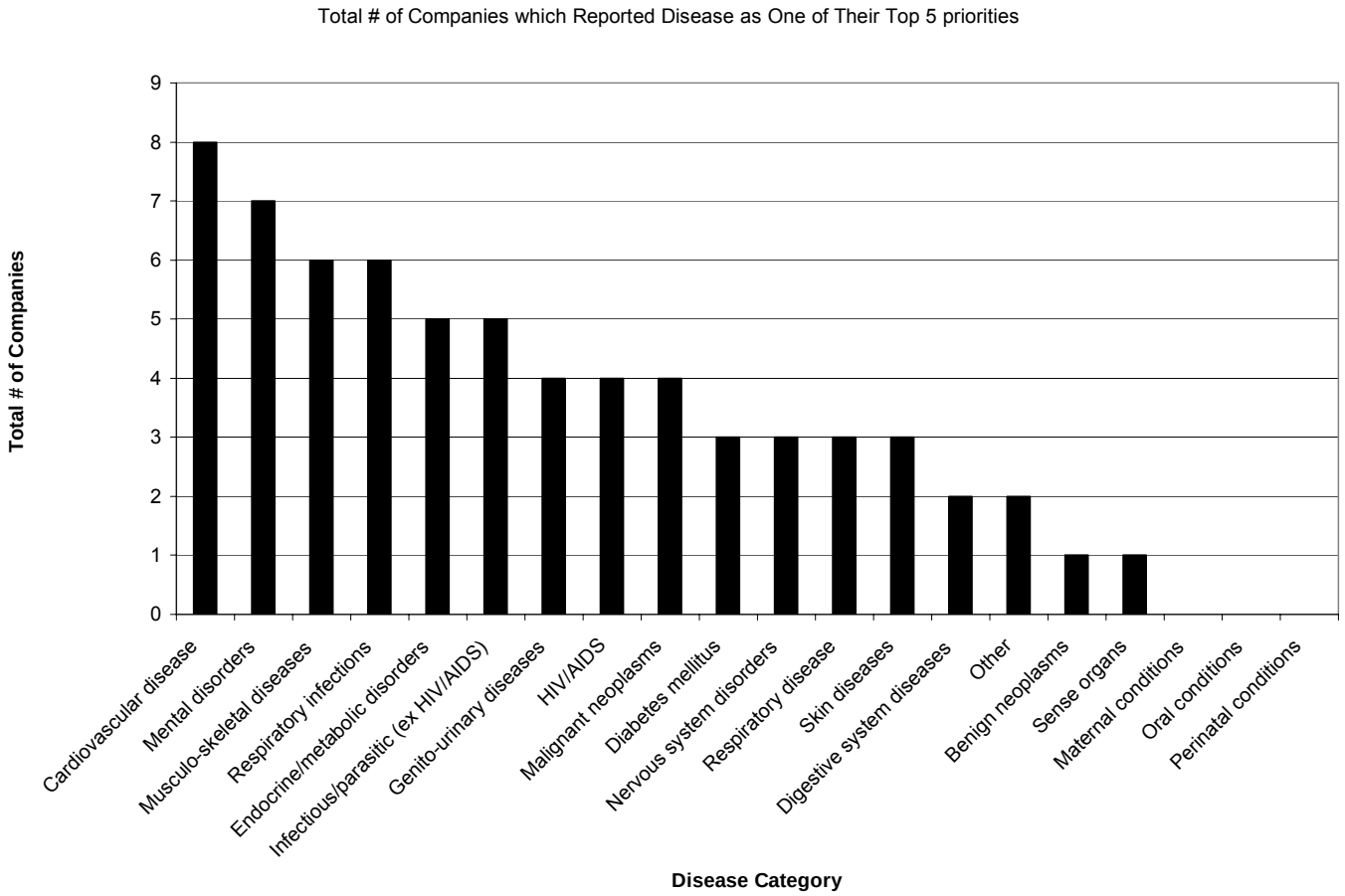
First, the descriptive and comparative analysis for Part One's quantitative results are presented, and second, Part Two's qualitative results are shown. Lastly, links between the quantitative and qualitative findings are described.

3.1 Descriptive Quantitative Results – Part One

The response rate was 70,86% (17 companies completed and returned a questionnaire out of 24 eligible companies) and the total number of trials reported was 214. The average number of trials per company was 12,59 and the median number of trials per company was 11 (interquartile range 7 to 20).

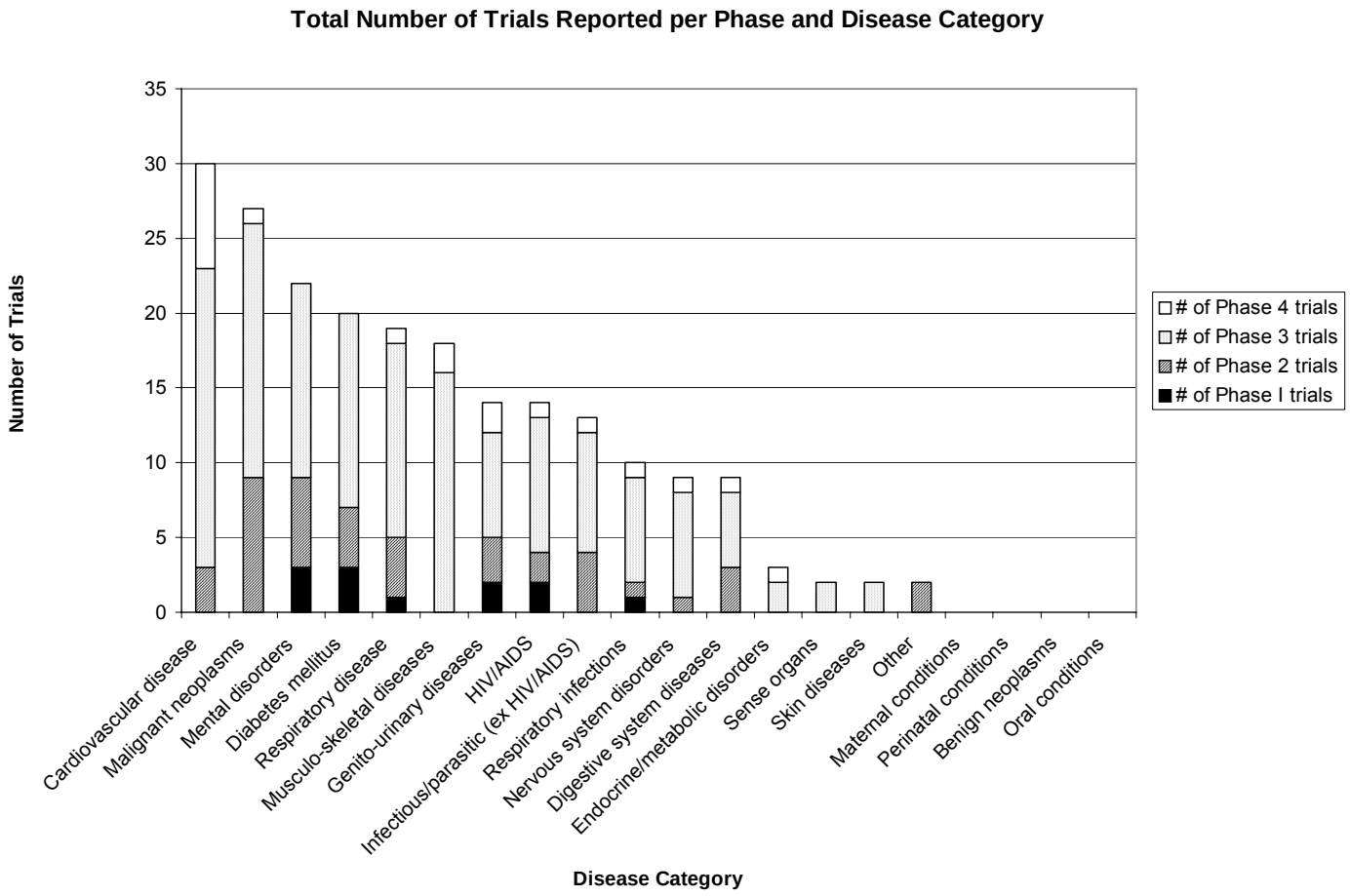
Of the 19 MRC disease categories plus one "Other" category for those diseases the MRC taxonomy did not capture, the leading diseases which companies reported on the questionnaire as one of their top 5 priorities were: cardiovascular disease, mental disorders, musculo-skeletal diseases, respiratory infections, endocrine and metabolic disorders, and infectious and parasitic diseases (excluding HIV/AIDS). Maternal, oral, and perinatal conditions were not identified by any company as one of their top 5 priorities *(Figure 1)*. The leading number of trials were in cardiovascular disease, malignant neoplasms, mental disorders, diabetes mellitus, and respiratory disease. No trials were reported for maternal, perinatal and oral conditions, or benign neoplasms *(Figure 2)*. Only two company priorities and two trials were categorised as "Other".

Figure 1: Total Number of Companies which Reported Disease as One of Their Top 5 Priorities



The highest number of Phase I trials were in diabetes and mental disorders, and for Phase II, malignant neoplasms and mental disorders trials were most numerous. For Phase III, the highest number of trials was for cardiovascular disease and malignant neoplasms, and for Phase IV, cardiovascular disease trials were the most numerous. No trials for maternal, perinatal and oral conditions were reported for any phase *(Figure 2)*.

Figure 2: Total Number of Trials Reported per Phase and Disease Category



For all trials, the total number of participants planned was 16 961, and the total number of participants enrolled was 23 200. A similar pattern of final numbers exceeding planned was found for sites (1 650 planned and 1 703 final sites). It appeared that companies not only met, but exceeded their expectations, or perhaps they underestimated the final number of patients and sites during their initial planning phase. Disease priorities in relation to the number of participants and sites showed that cardiovascular disease and musculo-skeletal diseases were the highest priorities, and no participants or sites were reported for maternal, perinatal and oral conditions *(Appendix 4 – Participants planned and enrolled, sites planned and final per disease category)*.

In summary, across measures of company research (company, trial, participant and site disease priorities), cardiovascular disease was the top priority, and maternal, perinatal and oral conditions were not reported as priorities. However, it is important to note that disease priority rankings differed considerably among the company, trial and participants planned measures of research as illustrated in Table 1 *(and seen for all other measures of research in Appendix 5 – Participants enrolled, sites planned and sites final numbers and rankings per disease category)*. For example, although diabetes ranked 10th for company priority and 8th for participants planned, it ranked 4th for trials; and HIV/AIDS ranked 7th for company priority and trials, yet it was 4th for participants planned. This reinforces the importance of clearly identifying which measure of research is being examined when reporting results as discussed in the literature review.

3.2 Comparative Quantitative Results – Part One

The extent to which pharmaceutical research in South Africa reflected the country's BoD was highly dependent on which measure of company research was examined (e.g., companies, trials, participants, sites, etc.) and which measure of disease burden was used as a comparator (e.g., Deaths, YLLs, DALYs). For example, Section 3.1 above showed how disease priorities differed depending on whether company or trial priorities were assessed. Disease priorities also differed depending on the MRC BoD measure considered (e.g., cardiovascular disease ranked 2nd in Deaths, 4th in YLLs and 6th in DALYS *(Table 2)*. Therefore, all available company research and BoD measures were compared, and trends and irregularities were the focus of the results.

Table 1: Company, Trial, and Participants Planned Numbers and Rankings per Disease Category

Company Priorities				Trial Priorities				Participants Planned Priorities			
Rank	Disease	# of Companies	% of Total Companies	Rank	Disease	# of Trials	% of Total Trials	Rank	Disease	# of Participants Planned	% of Total Participants Planned
1	Cardiovascular disease	8	47.06%	1	Cardiovascular disease	30	14.02%	1	Cardiovascular disease	4801	28.31%
2	Mental disorders	7	41.18%	2	Malignant neoplasms	27	12.62%	2	Musculo-skeletal diseases	1657	9.77%
3	Respiratory infections	6	35.29%	3	Mental disorders	22	10.28%	3	Respiratory disease	1509	8.90%
3	Musculo-skeletal diseases	6	35.29%	4	Diabetes mellitus	20	9.35%	4	HIV/AIDS	1402	8.27%
5	Infectious/parasitic (ex HIV/AIDS)	5	29.41%	5	Respiratory disease	19	8.88%	5	Infectious/parasitic (ex HIV/AIDS)	1161	6.85%
5	Endocrine and metabolic	5	29.41%	6	Musculo-skeletal diseases	18	8.41%	6	Genito-urinary diseases	1150	6.78%
7	Malignant neoplasms	4	23.53%	7	Genito-urinary diseases	14	6.54%	7	Respiratory infections	1084	6.39%
7	Genito-urinary diseases	4	23.53%	7	HIV/AIDS	14	6.54%	8	Diabetes mellitus	902	5.32%
7	HIV/AIDS	4	23.53%	9	Infectious/parasitic (ex HIV/AIDS)	13	6.07%	9	Mental disorders	874	5.15%
10	Diabetes mellitus	3	17.65%	10	Respiratory infections	10	4.67%	10	Malignant neoplasms	729	4.30%
10	Nervous system disorders	3	17.65%	11	Nervous system disorders	9	4.21%	11	Digestive system diseases	725	4.27%
10	Respiratory disease	3	17.65%	11	Digestive system diseases	9	4.21%	12	Endocrine and metabolic	365	2.15%
10	Skin diseases	3	17.65%	13	Endocrine and metabolic	3	1.40%	13	Nervous system disorders	351	2.07%
14	Digestive system diseases	2	11.76%	14	Sense organs	2	0.93%	14	Other	200	1.18%
14	Other	2	11.76%	14	Skin diseases	2	0.93%	15	Skin diseases	51	0.30%
16	Benign neoplasms	1	5.88%	14	Other	2	0.93%	16	Maternal conditions	0	0.00%
16	Sense organs	1	5.88%	17	Maternal conditions	0	0.00%	16	Perinatal conditions	0	0.00%
18	Maternal conditions	0	0.00%	17	Perinatal conditions	0	0.00%	16	Benign neoplasms	0	0.00%
18	Perinatal conditions	0	0.00%	17	Benign neoplasms	0	0.00%	16	Sense organs	0	0.00%
18	Oral conditions	0	0.00%	17	Oral conditions	0	0.00%	16	Oral conditions	0	0.00%

Table 2: MRC Burden of Disease Estimates, 2000

Estimates of DEATHS, YLLs, DALYs for all persons in South Africa, 2000											
Deaths				YLLs				DALYs			
Rank	Disease Category	Total	%	Rank	Disease Category	Total	%	Rank	Disease Category	Total	%
1	HIV/AIDS	165,859	29.8	1	HIV/AIDS	4,665,410	39.0	1	HIV/AIDS	5,067,490	32.8
2	Cardiovascular disease	92,201	16.6	2	Inf / para excl HIV/AIDS	1,331,432	11.1	2	Inf / para excl HIV/AIDS	1,490,399	9.6
3	Inf / para excl HIV/AIDS	57,502	10.3	3	Intentional injuries	1,066,136	8.9	3	Unintentional injuries	1,279,304	8.3
4	Malignant neoplasms	41,691	7.5	4	Cardiovascular disease	917,203	7.7	4	Intentional injuries	1,210,880	7.8
5	Intentional injuries	38,854	7.0	5	Perinatal conditions	907,199	7.6	5	Perinatal conditions	1,055,302	6.8
6	Unintentional injuries	30,076	5.4	6	Unintentional injuries	802,135	6.7	6	Cardiovascular disease	1,049,599	6.8
7	Perinatal conditions	27,361	4.9	7	Malignant neoplasms	499,257	4.2	7	Respiratory disease	729,442	4.7
8	Respiratory disease	23,009	4.1	8	Respiratory infections	456,093	3.8	8	Malignant neoplasms	520,883	3.4
9	Respiratory infections	22,340	4.0	9	Respiratory disease	265,329	2.2	9	Respiratory infections	467,062	3.0
10	Diabetes mellitus	13,157	2.4	10	Diseases of digestive system	197,322	1.6	10	Nervous system disorders	421,915	2.7
11	Diseases of digestive system	12,617	2.3	11	Nutritional deficiencies	190,970	1.6	11	Nutritional deficiencies	403,374	2.6
12	Genito-urinary diseases	8,049	1.4	12	Nervous system disorders	146,742	1.2	12	Diseases of digestive system	381,426	2.5
13	Nervous system disorders	7,160	1.3	13	Diabetes mellitus	145,421	1.2	13	Mental disorders	304,310	2.0
14	Nutritional deficiencies	6,488	1.2	14	Congenital abnormalities	128,676	1.1	14	Sense organs	249,936	1.6
15	Congenital abnormalities	3,859	0.7	15	Genito-urinary diseases	101,980	0.9	15	Congenital abnormalities	222,283	1.4
16	Endocrine and metabolic	2,109	0.4	16	Maternal conditions	56,806	0.5	16	Diabetes mellitus	175,849	1.1
17	Maternal conditions	1,875	0.3	17	Endocrine and metabolic	39,828	0.3	17	Genito-urinary diseases	149,718	1.0
18	Mental disorders	838	0.2	18	Cot death	16,294	0.1	18	Maternal conditions	101,300	0.7
19	Benign neoplasms	744	0.1	19	Mental disorders	14,379	0.1	19	Endocrine and metabolic	75,011	0.5
20	Cot death	491	0.1	20	Benign neoplasms	13,763	0.1	20	Musculo-skeletal diseases	45,681	0.3
21	Musculo-skeletal diseases	259	0.0	21	Musculo-skeletal diseases	4,655	0.0	21	Oral conditions	21,076	0.1
22	Skin diseases	48	0.0	22	Skin diseases	790	0.0	22	Cot death	16,294	0.1
23	Sense organs	--	0.0	23	Sense organs	--	0.0	23	Skin diseases	14,529	0.1
24	Oral conditions	--	0.0	24	Oral conditions	--	0.0	24	Benign neoplasms	13,763	0.1
	Other	--	--		Other	--	--		Other	--	--
	All causes	**556,585**			**All causes**	**11,967,822**			**All causes**	**15,466,828**	

NOTE: "Other" category taken out of ranking.
Source: Bradshaw et al. Initial Burden of Disease Estimates for South Africa, 2000. Cape Town: South African Medical Research Council, 2003.

Pearson and Spearman Correlation Results

Overall, there was a moderate association between pharmaceutical company research and South Africa's BoD as demonstrated by Pearson's and Spearman's rank correlation coefficients calculated for the measures of research and BoD. Differences in correlation strength were observed depending on the measure of research or BoD used. Most correlations were statistically significant and trends did emerge, although the small sample size of companies and limited number of disease categories did not result in statistically significant results across all correlations *(Table 3)*.

The range for Pearson's correlation coefficient was 0,30 – 0,61 (p=0,01 - 0,22), median 0,50. The strongest Pearson's correlation was for Participants Planned with Deaths (r=0,61, p=0,01), and for Sites Planned with Deaths (r=0,61, p=0,01). The weakest Pearson's correlation was for Companies with DALYs (r=0,30, p=0,22) *(Table 3)*.

The range for the Spearman's rank correlation coefficient was 0,28 – 0,57 (p=0,01 – 0,25), median 0,45. The strongest Spearman's rank correlation was for Participants Planned with Deaths (r=0,57, p=0,01). The weakest Spearman's rank correlation was for Companies with DALYs (r=0,28, p=0,25) *(Table 3)*.

Regardless of whether Pearson's or Spearman's rank correlations were calculated, the findings were very similar in that the strongest correlations tended to be for Participants Planned and Enrolled, whereas the weakest correlations tended to be for Company Priorities. It appeared as if companies' actions – evidenced by the number of participants they have in trials – were more in line with the BoD than what the companies stated their priorities were.

Also, across all Pearson and Spearman correlations, there was clearly a stronger association with Deaths, than with YLLs or DALYs. One interpretation of this is perhaps

that mortality data are more readily available and therefore used in priority setting. Research may be less in line with YLLs and DALYs because these composite measures are relatively new, not available or known.

Sensitivity Analysis – Correlations excluding HIV/AIDS

Because of the high BoD for HIV/AIDS across all MRC BoD measures, further analysis was performed that excluded HIV/AIDS from both Pearson's and Spearman's rank calculations. No substantial difference in the findings was apparent when HIV/AIDS was excluded. When HIV/AIDS was excluded, the range for the Pearson's correlation was 0,28 - 0,61 (p=0,01 – 0,26), median 0,51. With HIV/AIDS excluded, the range for the Spearman's rank correlation was 0,26 – 0,54 (p=0,02 – 0,29), median 0,45. These values are very similar to the correlations above with HIV/AIDS included *(Table 3)*. This demonstrates that with or without HIV/AIDS across both Pearson's and Spearman's rank correlations, pharmaceutical company research and South Africa's BoD was moderately correlated.

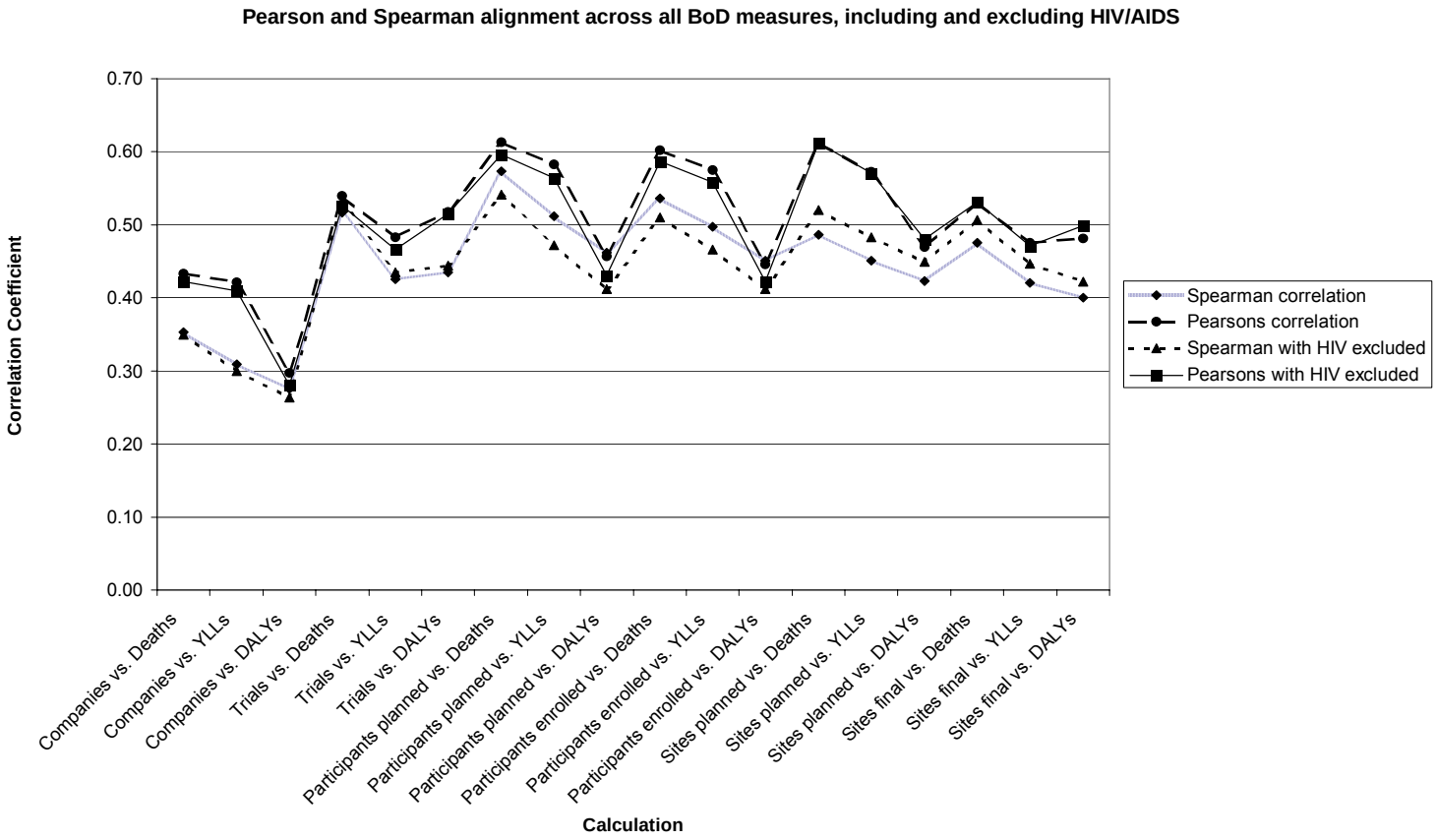
Table 3: Pearson and Spearman Correlations, including and excluding HIV/AIDS

Measure	Pearsons correlation	Pearsons p-value	Spearman correlation	Spearman p-value	Pearsons with HIV excluded	Pearsons with HIV excluded p-value	Spearman with HIV excluded	Spearman with HIV excluded p-value
Companies vs. Deaths	0.43	0.06	0.35	0.14	0.42	0.08	0.35	0.16
Companies vs. YLLs	0.42	0.07	0.31	0.20	0.41	0.09	0.30	0.23
Companies vs. DALYs	0.30	0.22	0.28	0.25	0.28	0.26	0.26	0.29
Trials vs. Deaths	0.54	**0.02**	0.52	**0.02**	0.53	**0.02**	0.53	**0.02**
Trials vs. YLLs	0.48	**0.04**	0.43	0.07	0.47	0.05	0.44	0.07
Trials vs. DALYs	0.52	**0.02**	0.43	0.06	0.52	**0.03**	0.44	0.06
Participants planned vs. Deaths	0.61	**0.01**	0.57	**0.01**	0.60	**0.01**	0.54	**0.02**
Participants planned vs. YLLs	0.58	**0.01**	0.51	**0.03**	0.56	**0.01**	0.47	**0.05**
Participants planned vs. DALYs	0.46	**0.05**	0.46	**0.05**	0.43	0.07	0.41	0.09
Participants enrolled vs. Deaths	0.60	**0.01**	0.54	**0.02**	0.59	**0.01**	0.51	**0.03**
Participants enrolled vs. YLLs	0.58	**0.01**	0.50	**0.03**	0.56	**0.02**	0.47	**0.05**
Participants enrolled vs. DALYs	0.45	0.06	0.45	**0.05**	0.42	0.08	0.41	0.09
Sites planned vs. Deaths	0.61	**0.01**	0.49	**0.03**	0.61	**0.01**	0.52	**0.03**
Sites planned vs. YLLs	0.57	**0.01**	0.45	**0.05**	0.57	**0.01**	0.48	**0.04**
Sites planned vs. DALYs	0.47	**0.04**	0.42	0.07	0.48	**0.04**	0.45	0.06
Sites final vs. Deaths	0.53	**0.02**	0.48	**0.04**	0.53	**0.02**	0.51	**0.03**
Sites final vs. YLLs	0.48	**0.04**	0.42	0.07	0.47	**0.05**	0.45	0.06
Sites final vs. DALYs	0.48	**0.04**	0.40	0.09	0.50	**0.03**	0.42	0.08
Median	*0.50*	*0.03*	*0.45*	*0.05*	*0.51*	*0.03*	*0.45*	*0.06*

BOLD **statistically significant**

In summary, across all calculations for company research and BoD measures, both the Pearson's and Spearman's rank correlations moved together, with or without HIV/AIDS as illustrated in Figure 3 below. This supports the consistency of the findings above because they are similar regardless of the correlation coefficient used.

Figure 3: Pearson and Spearman Alignment Across all Measures, including and excluding HIV/AIDS



Regression Analysis - Alignment and Gaps

Regressions of the actual values log transformed (not rankings) for all the measures of research and BoD were calculated *(Appendix 6 – Regression calculations across all measures)*. When the regressions were plotted in order to visualise which diseases were in alignment and which were not, regression graphs for those measures with **both** a Pearson's and Spearman's $p < 0,05$ revealed clear trends and formed the basis for identifying diseases in alignment and gaps - whereas there was too much variability to draw conclusions for those measures with a Pearson's and Spearman's of $p > 0,05$.

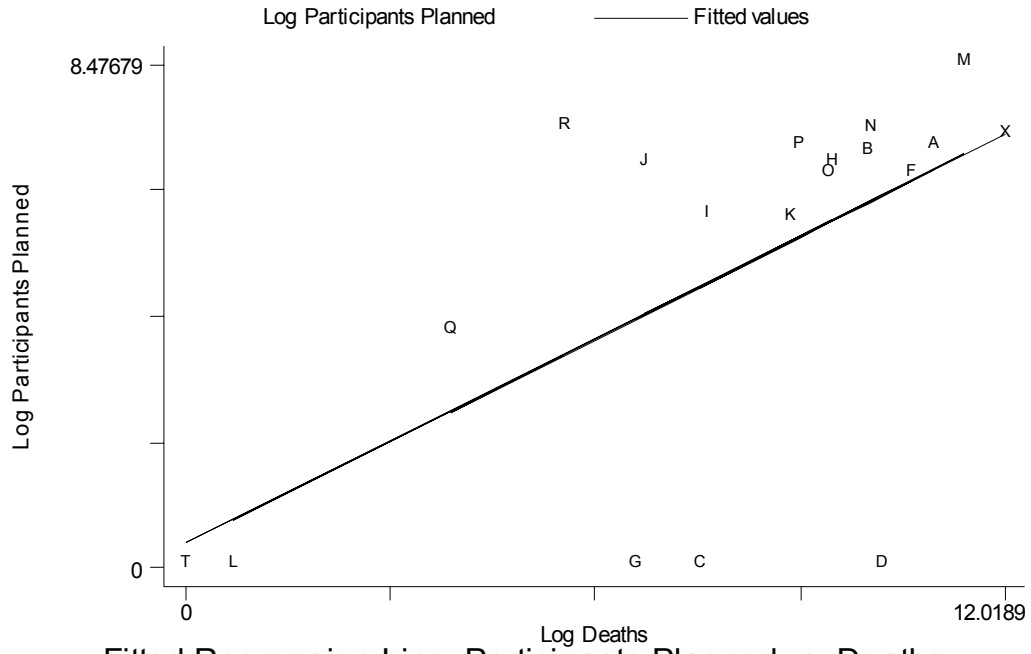
Measures with **both** a Pearson's and Spearman's $p < 0,05$ and plotted included:

- Trials vs. Deaths
- Participants planned vs. Deaths
- Participants planned vs. YLLs
- Participants planned vs. DALYs
- Participants enrolled vs. Deaths
- Participants enrolled vs. YLLs
- Sites planned vs. Deaths
- Sites planned vs. YLLs
- Sites final vs. Deaths

Gaps were identified when the disease category fell far above or below the regression slope line. Diseases above the regression line indicated an abundance of research. Diseases below the regression line suggested opportunities and need for more research. Alignment was identified when the disease category fell close to or on the regression line. The assumption for this analysis was that the regression line represented the ideal level for the measure of research (e.g., number of companies, trials, participants per disease) given the BoD measure *(Discussion)*.

For example, the regression graph *(Figure 4)* for Participants Planned vs. Deaths (Pearson's r=0,61, p=0,01 and Spearman's r=0,58, p=0,01) shows musculo-skeletal diseases (R) as the greatest gap above the regression line indicating an abundance of research, perinatal conditions (D) as the greatest gap below the regression line indicating opportunities for more research, and HIV/AIDS (X) and malignant neoplasms (F) near the regression line indicating alignment between Participants Planned and Deaths. Or, another way to interpret this regression graph is that fewer Participants Planned in relation to Deaths from musculo-skeletal disease (R) was anticipated by the regression line, and a higher number of Participants Planned was anticipated by the line in relation to the high number of deaths from maternal conditions (C). *(Figure 4 below, Appendix 3 for disease categories and codes)*.

Figure 4: Example Fitted Regression Line Graph - Participants Planned vs. Deaths



Fitted Regression Line: Participants Planned vs. Deaths

Aside from some moderate variation, across all regressions graphs for measures with a Pearson's and Spearman's of $p < 0,05$ consistent patterns of diseases in alignment and gaps with BoD measures were found *(Appendix 7 - Regression graphs for measures with Pearson's and Spearman's $p < 0,05$).*

An abundance of research was found for:

- Cardiovascular disease (M)
- Mental disorders (J)
- Musculo-skeletal disease (R)

Opportunities for more research were found for:

- Benign neoplasms (G)
- Maternal conditions (C)
- Oral conditions (T)
- Perinatal diseases (D), and

- Sense organs (L) (except for Trials vs. Deaths and Sites vs. Deaths where it was in near alignment).

Research in alignment was for:

- HIV/AIDS (X) (except for Sites where it was in near alignment)
- Infectious and parasitic diseases excluding HIV/AIDS (A)
- Nervous system disorders (K), and
- Skin disorders (Q).

Research in near alignment was for:

- Digestive disorders (O) (except for Trials vs. Deaths where it was in alignment)
- Diabetes mellitus (H) (except for Trials and Participants where it was abundant)
- Endocrine and metabolic disorders (I) (except for Trials vs. Deaths where there were opportunities for more research), and
- Malignant neoplasms (F) (except for Trials vs. Deaths where it was abundant).

The remaining diseases were all slightly above all regression lines, but not the farthest above. This indicated that there is more research in these diseases than expected in relation to the BoD measures, but not a clear abundance. These diseases include:

- Genito-urinary diseases (P)
- Respiratory diseases (N), and
- Respiratory infections (B) (except for Participants Enrolled vs. Deaths and Participants Enrolled vs. YLLs where it was abundant).

In summary, Pearson's and Spearman's rank correlation coefficients demonstrated that there was a moderate association between pharmaceutical company research and South Africa's BoD. Regression analysis determined which diseases had an abundance of, or opportunity for more, research, and also identified those diseases in or near

alignment with the country's BoD. Differences in association strength and degree of alignment were observed depending which measure of research and BoD were compared. However, clear trends were evident.

3.3 Qualitative Analysis of Company Priority Setting – Part Two

Part Two of the study described the process and timing of how pharmaceutical companies decide, plus which criteria they use, to prioritise in which disease category to conduct research in South Africa.

Process

All 6 interviewees shared that decision-making was cooperative between themselves at the local company affiliate level and their main office or headquarters. Organisationally, the headquarters did play a role in allocating resources and setting affiliate research priorities, but they were not the sole actor. Local affiliates in South Africa fulfilled a decisive function that included proposing research budgets and initiating or rejecting research projects. Five interviewees said the Medical Department had final say as to whether a trial would be conducted or not in the country.

Another major theme was that South African affiliates of global companies often had to compete with company affiliates in other countries to "get a trial". Four out of the six interviewees mentioned they have internal lobbying presentations that they deliver to senior medical management which highlight the strengths of the South African affiliate staff and their track record for delivering quality data on time and within budget.

Three interviewees raised the importance of dedicated local clinical staff in the decision-making process. They stated that the more clinical staff there is, the stronger the affiliate's role was in the decision-making process regarding whether or not to conduct a trial in South Africa. If there were little or no clinical staff, interviewees explained that

research was out-sourced, or temporary contract clinical staff was hired, and the affiliate had less of a role in the decision-making process for trials. The questionnaire in Part One revealed that the majority of companies did have dedicated clinical staff (14 out of 17 companies) and the total number of dedicated clinical staff reported for all companies was 146,5 people. This supports the interview findings that decision-making was cooperative with headquarters as the majority of participating companies had strong local clinical departments.

Timing

The overall timing to conduct a clinical trial (including deciding, planning, receiving in-country regulatory and ethics approval, implementation, and final data analysis) was identified by all interviewees as a critical factor in deciding whether or not to conduct a trial in South Africa. They explained that molecules that were discovered years ago are only now coming to the trial phase and it can take up to 15 years from a drug's discovery to reach patients. Therefore, there is extraordinary pressure on industry to deliver new discoveries, and quality trials conducted in a timeous manner are essential.

The range of time estimated by the interviewees for the decision-making process by its headquarters (whether or not to initiate or approve a trial in a specific country) was 3 to 6 months. The local decision-making by the South African Medical Directors and the affiliate (whether or not to accept or initiate a trial in South Africa) ranged from 1 to 6 weeks.

External regulatory approval times for clinical trials were reported to be 3 to 5 months from the date of submission to the South African Medicines Control Council (MCC). All interviewees explained that the MCC only meets periodically so an additional 2 months frequently had to be added to the timeline while companies wait for the next MCC meeting. Eastern Europe was often raised by interviewees as a major competitor to

South Africa because of their respective regulatory authorities' ability to timeously approve trials and the strength of their scientific community.

All interviewees recognised that both company and regulatory authorities impact the total timeline. Two people mentioned that individual companies were actively trying to improve their own decision-making timelines, and explained that there was industry-wide support of the MCC's effort to improve clinical trial approval timelines.

Criteria

Criteria for decision-making focused on feasibility, market, and environmental facilitating and constraining factors. BoD also played a role, but with some caveats similar to those limitations identified in the literature review.

Feasibility

When asked what criteria companies use to prioritise research, feasibility concerns were the immediate response from all interviewees. Feasibility included: company, affiliate, and external investigator expertise; the availability of participants and sites; and cost and time required.

All companies considered in-house expertise on how to conduct clinical trials a facilitating factor (e.g. how to recruit patients, work with external investigators, manage complex data sets, and comply with ethical rules). Companies felt that they had this expertise for the most part which was relevant to their decision to conduct trials because they could do so within their current resources. This was supported by the questionnaire findings, which showed that the majority of companies in this study had dedicated clinical staff (14 out of 17 companies). Furthermore, only 47 out of the 214 trials were contracted out (22%), while 166 were conducted in-house (78%), and 1 trial was not reported in the questionnaire.

All interviewees raised the significance of company expertise (e.g., their internal research infrastructure, human and financial resources, and research track record in specific disease areas). One interviewee pointed out that "a company can only do trials if a product has made it through its discovery pipeline" which referred to the challenge of research not simply being about identifying a disease target, but also being successful in finding a promising preventive or curative intervention.

Overall, interviewees praised external investigators' scientific rigour and were proud of South Africa's excellent reputation for quality research. It was explained that external investigators are critical to clinical trials because they are the ones who actually see the participants, provide the treatment, adhere to ethical guidelines, and fill in all the paperwork for the company's clinical staff to then analyse. However, the availability of experienced investigators was raised by two interviewees as a growing concern. Potential reasons put forward were that there may be a growing amount of trials for the number of investigators, and that there may be fewer experienced investigators because many have emigrated and new ones have not yet been trained.

The availability of participants and sites was reported by all to be a facilitating factor and was inexorably linked to the BoD in the country. Since South Africa has both "developed" and "developing" world diseases as noted in the literature review, there are more diseases that can be researched in the country, which was attractive to companies.

Lastly, cost and time were raised as feasibility factors. All interviewees said that South Africa was competitive against other countries when it came to costs, but there were concerns with regulatory approval timelines as discussed above.

Market

Only a few interviewees brought up market issues unprompted. Although when prompted, all interviewees expressed that marketing concerns did play a central role. Interviewees explained marketing opportunities were very much linked with the BoD. Simply put, if a disease is prevalent there is a potential market for sales. However, four interviewees explained that the market is changing in South Africa to include more than just the 7m people with existing medical aid coverage, and reaching toward covering all 43m citizens, through a growing private insurance market and expanding public coverage. They highlighted that this expanding market is relevant to companies' decisions to research in the country because it potentially provides a better return on their investment with greater sales opportunities in both the private and public markets.

Furthermore, it was elaborated upon by one interviewee that the market size is also a function of whether the patient, government or private insurance-based medical scheme is willing and able to pay. It was explained that purchasers were reluctant to pay for life-enhancing medicines (e.g., urinary incontinence) because they tended to focus only on those diseases with high mortality where they can see an immediate benefit from the medicine. Also, treatments for chronic diseases (e.g., hypertension) encountered various hurdles, such as restrictive treatment guidelines, prescribing limitations, pre-authorisation by the payer, and exclusions from formularies based only on immediate cost and not long-term cost-benefit analysis. These obstacles also played a role in companies' decision on how large the potential market may be, and therefore whether to conduct a trial in South Africa or not.

Three interviewees reported that if a low marketing opportunity were identified, yet the BoD was high, their headquarters would consider supporting local trials, both financially and with human resources (e.g., HIV/AIDS trials).

Results from the questionnaire illustrated that companies determined they do have a market for most of their products in trials. The majority of trials (140 out of 214, 65%) were for products that companies were seeking registration for in South Africa, 53 trials (25%) were with products already registered, and 13 trials (6%) were for products not seeking registration. New MCC trial approval criteria introduced in 2000 may have contributed to the high number of trials for products seeking or already having registration because the MCC requires companies to state whether they are seeking local registration, why the product is needed, and how it will benefit South Africans (MCC 2003a). However, interviewees had the impression that these criteria were not consistently applied, and more importantly, felt that companies sought registration for their products because of the potential market, and not because of MCC requirements.

Environment

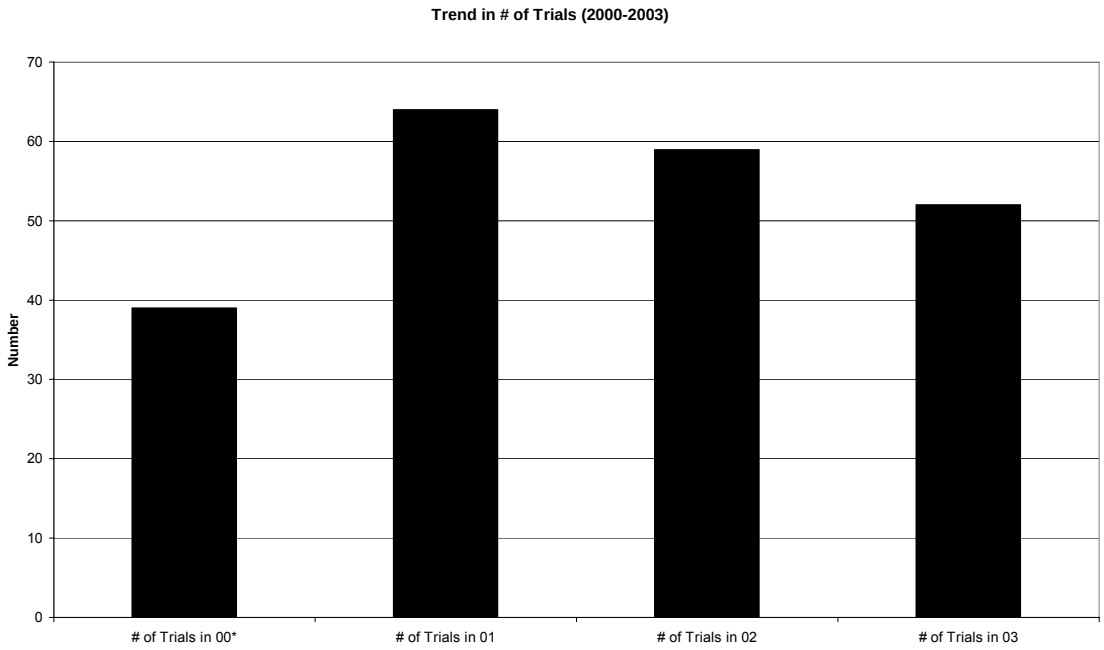
The importance of a pro-research environment was raised by all interviewees. In addition to the feasibility factors outlined above, interviewees identified the need for a strong scientific infrastructure that supplies researchers and services, and a supportive government that attracts and fosters research initiatives. Although interviewees did not specifically comment whether the scientific infrastructure or government support was a facilitating or constraining factor, they alluded that these factors could be part of the reason why companies were not pursuing pre-clinical research (3 out of 17 companies reported pre-clinical work in the questionnaire) and that most companies focused on later stage Phase 3 trials *(Table 4 and Definitions)*. It was explained that discovery research (pre-clinical and early phase research) was highly dependent on well-trained scientists and adequate facilities, as well as the enforcement of strong intellectual property laws to protect new discoveries. The fact that companies are not investing in discovery research or early phase clinical trials is perhaps an indication that there is potential to attract this type of research to South Africa.

Table 4: Total Phases of Trials Reported

	# of Phase 1 Trials	# of Phase 2 Trials	# of Phase 3 Trials	# of Phase 4 Trials	Total Trials
#	12	42	141	19	214
%	5.61%	19.63%	65.89%	8.88%	

Interviewees also suggested that environmental factors may be the reason why this study found the overall number of trials was declining *(Figure 5)*. It is unclear what factor, or combination thereof, is specifically driving this trend and further analysis of this is outside the scope of this study.

Figure 5: Declining Number of Trials



*may be underreporting in 2000

Two interviewees also mentioned that an important facilitating environmental factor was the international recognition of the South African MCC because trials conducted in South Africa were eligible for approval in the European Union and the United States. This enabled companies to include South Africa in their global research initiatives.

A constraining environmental factor identified was a generally negative attitude toward pharmaceutical research in the country. Specifically, interviewees raised concerns that negative conceptions about industry research, such as assumptions about using people as 'guinea pigs' in trials and 'industry only caring about profits' (quotes from interviews)

undermined the benefits of research. They listed these as creating life-saving and life-enhancing medicines for unmet medical needs, building and supporting the research infrastructure in the country through creating jobs and attracting foreign investment, linking South Africa with the global research community, and providing access to new treatments through trials and post-trial care which otherwise would be inaccessible.

Burden of Disease

All interviewees said that the use of BoD measures (Deaths, YLLs, DALYs or other measures such as prevalence and incidence) was part of their decision-making process, but not a sole criterion. As described above, it was explained that other factors such as feasibility, market and environment played a crucial role, and are inexorably linked to BoD. For example, if the BoD is significant, so will be the number of participants for trials, as will be the potential market.

Furthermore, three interviewees highlighted dangers of focusing just on BoD as a criterion for research. Smaller companies were especially concerned about using BoD as a sole criterion because they felt that they should not be penalized if they do not happen to have expertise in an area of the greatest burden. One interviewee said, “Not all companies can specialise in the top burdens, and we all need to find our niche. We don’t want to be penalised for specialising”.

Another interviewee raised similar concerns for people living with orphan diseases (those diseases that are not common, e.g., growth hormone deficiency) or a disease deemed to be of lower burden (e.g., glaucoma). The interviewee said that if pharmaceutical research were targeted to only those diseases with the greatest burden, those people who do not have a high-ranking disease would be at a disadvantage.

The majority of interviewees raised concerns about maintaining the competitiveness of South African researchers if research only focused on top disease burdens. An example was given that South Africa's globally recognised leadership in laser eye surgery would have never happened if public and private researchers were restricted to investigating only top burdens of disease. Furthermore, interviewees said that delaying or not approving trials for low burdens of disease or life-enhancing drugs would limit South African investigators' ability to participate in the international research community which might be focused on diseases that may not be as prevalent in South Africa yet. It was suggested that South African researchers in these fields would become frustrated and pursue their work elsewhere.

Lastly, four interviewees suggested that using BoD as a core criterion for prioritising pharmaceutical research was short-sighted. They explained that today's available BoD data reflects yesterday's diseases due to the time lag in data collection, and research should not focus only on today's problems, but anticipate what tomorrow's future health challenges will be. One interviewee said, "in 5 years down the line hopefully we can look at other diseases [besides HIV/TB]. The prevalence and incidence of emerging diseases will change. In '98, the focus on breast cancer was huge. Now it's under control. Today's issue is HIV. Tomorrow who knows?" Furthermore, all interviewees expressed that pharmaceutical research extends beyond just meeting a country's BoD to developing the country's research capacities and international competitiveness.

In summary, the qualitative interviews revealed that feasibility, market forces and overall research environment issues were all important in the prioritisation process for companies. Also, the BoD, although an important criterion, was not the sole criterion, and there were concerns with relying on it as an ideal benchmark for research in the country because of its limitations.

3.4 Link Between Quantitative and Qualitative Results

The quantitative results of Part One of this study that identified gaps and alignment between pharmaceutical company research and South Africa's BoD are best interpreted with the qualitative findings of Part Two that explored the process and criteria companies use to decide their research priorities.

Gap areas that were identified may have been indicative of other factors aside from BoD playing a role in companies' decision-making process. For example, the abundance of research in cardiovascular disease, mental disorders and musculo-skeletal disease appeared to be in excess of the MRC's current BoD measures. If BoD were the sole comparator for the "right" amount of research, one conclusion could be that less research should be devoted to these diseases. However, based on the interviews, companies do not make decisions purely on the basis of current BoD. Rather, it seems likely that these diseases were chosen because they were more feasible to conduct trials, the market was more promising, and companies anticipated the future BoD to include these diseases.

For those gap areas with opportunities for more research, such as perinatal diseases and maternal conditions, these diseases appeared to be grossly under the MRC's current BoD measures. Again, if BoD were used as the sole "gold standard", one conclusion could be that more research should be devoted to these diseases. Or, another conclusion given the multi-faceted nature of health priority setting arising from the interviews could be that industry's lack of research in these areas might be a reflection of difficult feasibility issues such as access to participants for clinical trials, or environmental considerations such as the prominence of other determinants of poor health for these disease burdens such as nutrition and sanitation. Or, these gaps could be a result of industry's perceived lack of market for maternal and perinatal conditions.

For areas in alignment, such as HIV/AIDS and infectious and parasitic diseases (excluding HIV), they appeared to be on target with the MRC's current BoD measures. Therefore, one could conclude when using BoD as a sole criterion, that the "right" amount of research is being conducted in these diseases. However, since the interviews showed that companies do not look solely at BoD, any alignment between research and BoD may be happenstance and the feasibility, market and environmental issues may have been such that they encouraged companies to conduct trials in the these specific burdens of disease. Facilitating factors for research that these diseases in alignment shared in common merit further exploration because these characteristics could then be used encourage private pharmaceutical company research in other diseases of need.

In conclusion, although the quantitative findings revealed alignment and gaps between pharmaceutical company research and South Africa's BoD, the interviews supported the literature review findings that health priority setting is multi-faceted and not one criterion, such as BoD, is solely relied upon. Therefore, it is important to recognise the limitations of relying on BoD measures as a "gold standard" comparator for pharmaceutical company research. However, the results of this study remain instructive pending the development of other comparators and methodologies. Furthermore, the qualitative results of this study may point to policy actions that can be taken to better leverage private pharmaceutical company research to meet public health needs.

4.0 Discussion

This study reveals the complexities of encouraging pharmaceutical company research in South Africa in areas of health need by blending a quantitative analysis which identified alignment and gaps between pharmaceutical research and the country's BoD, with a qualitative description of the process and criteria companies use to prioritise their research. This two-fold approach enables a more robust interpretation of the results that adds to the existing body of knowledge on health research priority setting. Furthermore, the implications of these findings can impact current policy and practice, whilst recognising the study's limitations.

4.1 Results in Relation to Existing Literature

Knowledge of pharmaceutical company research priorities

Based on trends found in the international literature, it was anticipated that pharmaceutical research in South Africa would not be in line with the country's BoD as was found in other countries (Comanor 1996; Michaud and Murray 1996; MSF/DND Working Group 2002; Yamey 2002). However, this study reveals that overall there is moderate alignment between pharmaceutical company research in South Africa and the country's BoD. Furthermore, the findings go beyond existing aggregate studies and specifically identify diseases in alignment and gaps with the country's BoD. It is recognised that this study did not capture research outside of the country; however, this study does provide a previously unknown baseline and is an important step toward leveraging private pharmaceutical company research in South Africa to meet public health needs.

Understanding priority setting processes

The first key issue identified in the literature review, which was the need to recognise various stakeholder objectives when examining priority setting, was not specifically raised in the interviews. However, it is important to point out that there were two distinct perspectives on this study that emerged anecdotally prior to its start. Most public health and government experts I informally consulted assumed this study would prove the industry was not focusing on needs of South Africa, whereas most industry people thought they do focus on the needs of the country - otherwise they would not have a business. Although the literature also suggested that public health objectives to reduce overall BoD and private industry objectives to provide medicines to a consumer market may clash, the results show that their objectives can be complementary. For example, the company research priorities in alignment with South Africa's BoD, such as HIV/AIDS and infectious diseases, informs us that these diseases are priorities for both parties. However, this study reveals that the rationale for choosing these targets may differ. Public health officials may deem it a health need based on BoD, while companies may deem it a research priority where trials are feasible, the market is attractive and the overall environment for research is supportive. For those areas of company research that are not in alignment with the BoD, such as cardiovascular disease where research is in abundance, or maternal conditions where there are opportunities for more research, this study goes beyond existing literature. This study not only points out these gaps, but provides policy makers additional insight on ways to encourage research in diseases of need that incorporate companies' objectives and the criteria they use for priority setting so as to maximise private company research to benefit public health.

The second key issue identified in the literature review, namely that health priority setting is complex and multi-faceted, was clearly supported by the findings of this study which revealed the importance of feasibility, market, environmental issues and BoD in

company decision making. However, these findings differ from some assumptions identified in the literature review that stated research was primarily driven by headquarters marketing personnel and global profit strategies (MSF/DND Working Group 2002; Resnik 2003). Specifically, feasibility and environmental issues tended to dominate the interviews more so than market influences. This was perhaps because Medical Directors were interviewed and they came from the medical perspective of practically getting the trials done. This complex set of criteria furthers our understanding of why some company research priorities are in alignment with disease burdens and others are not because it is apparent that there are more factors involved in priority setting than just BoD. However, what is not well known is the weighted importance of the various factors in decision-making, which was outside the scope of this study.

Methodological aspects

The third key issue that emerged from the literature was the limitations of relying solely on BoD as a comparative indicator for pharmaceutical company research. Similar concerns were echoed in this study's findings and include:

- Medicines are not the only solution to reducing BoD

  This study's major assumption is that medicines reduce the BoD. As doctors and patients alike may attest, pharmaceuticals can play an important role, but the interviewees pointed out that medicines are not the only solution to reducing BoD. Gilbert also raised this concept in her article about other determinants of health that may have an even stronger influence on BoD such as environmental pollution that can aggravate asthma, social inequalities that can lead to increased HIV/AIDS rates, gender inequalities that can result in rape, economic stress that can induce high blood pressure, and crime that can multiply injuries (Gilbert, Selikow, Walker 2002). Bradshaw et al advocated, "all role players, including government, pharmaceuticals, business, NGOs and the community need to give urgent attention to this [burden of

disease]" (Bradshaw et al 2003a, xi) in recognition that one intervention alone can not effectively reduce a country's burden of disease. Furthermore, Mrazek and Mossialos pointed out that, "stimulating research and development for neglected diseases is important as part of a wider long-term public health strategy and must be addressed simultaneously with resolving more immediate problems of access to medicines and health system sustainability in less developed countries" (Mrazek and Mossialos 2003, 75).

- Changing burdens of disease

This study's findings also reflected Varmus' concern found in the literature that policy makers should not just focus on today's health challenges, but need to consider future burdens (Varmus 1999). Interviewees' mention of the 15-year lag time between drug discovery and delivery of a new medicine to patients is an indication that companies focus their research on tomorrow's diseases, and not just today's. Furthermore, given the unpredictability of discoveries, one never knows what findings today in an "unimportant" area (e.g. toenail fungus) can impact a very serious disease tomorrow. Moreover, the abundant areas of research identified in this study may be the highest burden of disease in the future (e.g., growing cardiovascular disease needs). Therefore, given that BoD measures are calculated from historical data, they may neglect to anticipate what tomorrow's health problems will be.

The changing BoD pattern is especially relevant for South Africa. Not only does South Africa face developed and developing world health challenges (Bradshaw et al 2003b, 1), it is undergoing an "epidemiological transition [that] includes changes in the cause of death patterns and overall changes in health and disease that occur during socio-economic transformation" (Bradshaw et al 2003a, 2). For example, "it is estimated that the South African population 60 years and older was 2.9 million in

2000, constituting 6.4% of the total population. These figures are estimated to increase to 3.95 million and 8.4% in 2010" (Joubert, Nannan, Bradshaw 2003, 155). Therefore, it would be short-sighted to limit scientific discovery to only what is deemed important today.

- Unintended consequences of relying on BoD

The interviews also revealed two limitations of relying on BoD that were not found in the literature. First, all companies do not have the capacity to specialise in all the top disease priorities. This was reflected by the concerns of smaller companies that did not want to be penalised or hindered from conducting research in their niche areas because they do not happen to reflect the country's BoD. Furthermore, having all companies focus on top BoD would not be very efficient because each would be duplicating the other's efforts. Second, the interviewees pointed out that if pharmaceutical research were targeted at only those diseases with the greatest burden, those people who do not have a high-ranking disease would be at a disadvantage. This is intuitive because if something is chosen as a priority, this means something else is not – which is the underlying challenge of priority setting because not all diseases can be priorities.

The fourth key issue raised in the literature was the need to compare multiple measures of research and BoD with a variety of statistical tools in order to have a more complete representation of their relationship. Otherwise a study's findings could be misleading. Therefore, this study intentionally expanded upon previous methodologies found in the literature in that it deliberately examined multiple measures of research and BoD with statistical analysis of both rankings (Spearman's correlation coefficient) and actual values (Pearson's correlation coefficient and regressions). Furthermore, this study generated new measures of research according to company, trial, participant and site priorities. These measures broke away from the traditional study design that focused on the use of expenditure as a measure of company research (PMA 1997, Wits Health

Consortium 2000, Department of Science and Technology 2003). Firstly, this was because expenditure data per disease was difficult to access, and secondly, it was decided that these unique measures were a better indication of company research activity. This study was also the first known comparative analysis that used all three of the MRC's new BoD measures (Deaths, YLLs and DALYs). These methodological advances and knowledge gained through this exercise may enable other researchers to conduct similar analyses to compare BoD with other areas of health, such as numbers of medical personnel or patient access to care.

4.2 Impact on Policy and Practice

This study's findings can enable both public and private decision-makers to generate realistic policies to encourage pharmaceutical company research in areas of need. The results indicate that strategies that are beneficial to public, private and other stakeholders are the most feasible and cooperation among the sectors is vital for all parties to meet their respective objectives. For example, companies need public health officials to identify areas of unmet medical need, create sustainable health care systems to deliver medicines, and foster favourable research environments. Public health officials need companies to discover and develop new medicines to prevent or treat unmet medical needs and provide them at accessible prices on both public and private markets. The multi-faceted nature of company research priority setting described in this study complicates policy making because there is no simple framework that can be applied. Therefore, a combination of strategies may be necessary.

First of all, the results of this study show that in order to leverage private pharmaceutical company research to benefit public health, companies need to be enticed to make choices that are good for both their business and public health. Directing research toward areas of need by either asserting that companies should be benevolent (Isaakidis et al 2002), or hindering or preventing companies from researching what they choose

may have the opposite effect and drive research away from diseases of need or out of the country. This sentiment was echoed by the former head of the US National Institutes of Health (NIH) who objected to US Congressional directives to guide research priorities in the public sector because of the multi-faceted nature of allocating research dollars (Varmus 1997). One could assume that such mandates would be highly controversial in the private sector too because as the interviews revealed, other factors such as feasibility, market and the overall environment are important to industry decision making. Furthermore, the study's findings show that South Africa competes with other countries for industry research and such a punitive approach to increasing research would potentially have negative consequences and reduce research in priority disease areas because companies can conduct their research elsewhere.

Secondly, a combination of "push" and "pull" strategies aimed at companies, and infrastructure development aimed at countries, emerged from the international literature as the most feasible way to stimulate pharmaceutical research in areas of need. Widdus explained, "Push interventions to lower the costs and risk of product development for industry, with pull interventions providing economic and market incentives, and the creation of infrastructures allowing products to be put into use" (Widdus 2001, 713). Reich further outlined four common "types of fixes" for when there is a need for more research in unmet medical needs: 1) public subsidies through national and international organisations, 2) new public-private partnerships which combine the skills of private researchers with public health experts, 3) protection of product patents in developing countries to create incentives for the private sector, and 4) the creation of 'purchase funds' or guaranteed markets for future products" (Reich 2000, 1980). Other authors made additional infrastructure oriented suggestions such as the creation of capacity-building programmes for researchers, government funding of basic research, government policy coordination among trade, health, finance, and justice, and development of a sustainable health care system. Other "pull" suggestions were the

creation of markets with tiered pricing, and rewards of patent-life extension in a "Western" market for the development of a drug for a neglected disease (Erill 1998; Resnik 2003; Webber 2003; Wolffers, Adjei, van der Drift 1998).

This push/pull approach incorporates strategies that would not only assist in attracting research to high burdens of disease which hopefully would result in more prevention and treatment options, but would also support other public health objectives such as improving access to health care and sustaining scientific and academic infrastructures. These strategies would also meet the private sector objective to provide medicines to a larger market because companies would better meet the needs of more people, while at the same time the strategies would enhance the feasibility and timing of trials and foster an environment that welcomes clinical research.

However, a potential conflict emerges between pharmaceutical company research and a country's burden of disease when strategies cannot be identified that would make clinical trials more feasible, the market more attractive, or the overall research environment supportive enough to attract company research on specific disease. In this case, it may be necessary for policy makers to tap into other sources of research such as government or non-governmental organisations. For example, as recognised by the leaders at the US National Institutes of Health, "complementary activities in other agencies…[and] in the pharmaceutical and biotechnology industries…may favor the expenditure of NIH dollars on relatively rare diseases, with low values for the BoD, as measured in terms of disability-adjusted life-years, for which there is little incentive for research and development in the private sector" (Varmus 1999, 1914). In Gross et al's study comparing NIH funding with BoD in the US, they further elaborated that "although research performed by industry may be distinct from NIH-funded research in a number of ways, it is important for policy makers to consider these substantial efforts when allocating [public] funds" (Gross et al 1999, 1885-1886). This was evidently in

recognition that company research can be leveraged for certain diseases, and where they cannot, other resources need to be employed. However, regardless of whether for-profit companies, government, or non-profit organisations conduct research, the feasibility of trials, the source of funding (be it profit, taxes or donations), and an overall supportive research environment still needs to be in place.

The literature revealed that many countries have implemented specific programmes to encourage pharmaceutical research such as the European Union's Sixth Framework Programme for Research and Technological Development (2002-2006) (Bjerrum 2002). Other incentives programmes have been created in Japan, Australia, India, Spain, China, Ukraine, Ireland, United Kingdom and South Korea (SCRIP 2003a-e, 2001a-b, 2000a-b).

These efforts to foster pharmaceutical research raise two questions. First, why would a country be interested in persuading companies to conduct research in the country? And, second, does research on country-relevant diseases need to take place in the country when such research could theoretically take place anywhere? Webber proposed an answer to the first question and outlined "benefits of pharma R&D [research and development] for host countries" which include:

- Establishment of high value-added, high technology sector; industry diversification
- Contribution to economic growth and trade surplus
- International credibility and a raised country profile as host to high technology investment across a broader front
- Development and commercialization of public sector research
- Increase potential inward investment and joint ventures
- Better access to modern technology and information and technology transfer

- High quality jobs – deployment of graduates/PhDs from university
- Reduce or limit brain drain
- Improved healthcare through access to newer medicines
- Country capacity to understand and use state-of-the-art science, and maintain public confidence
- Tackle country-specific disease/medical problems
- Contribution to global public good"

(Webber 2003, 9-10)

With regard to the second question, Webber points out the benefit of being able to "tackle country-specific diseases, (2003, 10)" but he does not limit a country's research scope to country-relevant diseases. Webber recognises that the infrastructure and capacity building benefits of research extend well beyond just meeting a local health need, and attracting any research can improve the overall social, political, economic and social climate of a country.

On the other hand, Comanor argued that, "Research and innovation may be influenced by their geographic location to the detriment of patients and consumers in lands where these efforts are not undertaken" (1996, 205). This thinking supports the concept that one should attract in-country research on country-relevant diseases with the assumption that if a country does not research country-relevant diseases, there is no guarantee that somebody else will. This is evidenced by the numerous multi-country and intersectoral partnership initiatives that have been launched with the aim of developing and providing drugs for neglected diseases such as the new Drugs for Neglected Diseases Initiative (DNDI). (Nelson 2003; Butler 2002; SCRIP 2002; Gelband and Trouiller 2002; Mrazek and Mossialos 2003). Although no single country is driving the process, the trials for these new drugs are predominantly in countries affected by neglected diseases because that is where the patients, and respective burden of disease, are located.

Therefore, there is not clear agreement on whether there should be a link between in-country research and a country's burden of disease. However, as discussed in the literature review, many recent studies did examine in-country research in relation to a country's burden of disease as a starting point for priority setting, which informed the design of this study. With respect to South Africa, the country is unique because it's "own diseases" are both of the developing and developed world and its disease profile is changing (as noted in the literature review). It also has an excellent foundation and capacity for research. As a result, South Africa is perhaps in a good position to assume a leadership role in clinical research on its country-relevant diseases which would not only benefit developing countries on the African continent and beyond, but also developed countries. Furthermore, research on country-relevant diseases may allow for the further advancement of local expertise in diseases that affect South Africans, and therefore potentially improve the local health care system's ability to treat such diseases. However, this is not to say that research on country-relevant diseases should be to the exclusion of other research. Given the potential benefits of any research outlined by Webber above, South Africa's changing disease profile, and its promising leadership position in global clinical research, it would be advantageous for the country to attract as much research as it could. If, then, South Africa would like to leverage pharmaceutical company in-country research for its diseases of need, this study provides a starting point for that discussion.

South Africa has recognised these opportunities and has taken steps to encourage pharmaceutical research. The National Drug Policy for South Africa stated that drug research and development is a priority. "Research aimed at alleviating common diseases and complaints will be encouraged, eg the development of new, less toxic, more effective and more stable drugs and vaccines for existing conditions" (DoH 1996, 24). A pharmaceutical investment study commissioned by the Department of Trade and industry (DTI) sought to describe facilitating and constraining factors for pharmaceutical

research, development and manufacturing in the country and further assessed South Africa's international competitiveness (CMCS 2001). It was also estimated by DTI that South Africa currently attracts R1 billion/year in foreign capital investment/year for pharmaceutical clinical research, and has the capacity for R3,6 billion (Bisseker 2002, 1). South Africa's excellent research track record, especially for pharmaceutical company clinical trials, has been recognised internationally, and its "solid reputation for clean data on time at competitive prices has made it a comfortable place for multinationals to conduct trials for the past two decades" (Bisseker 2002, 1). Furthermore, the country was described as well positioned for research because of its intellectual capacity, competency in medical practice, academic investigators, availability of participants, favourable local trial costs, and solid long-term relationships between sponsoring companies, academic institutions, private investigators, and the Medicines Control Council (MCC) (Haus 2001b, 49). Attracting more research to South Africa and supporting current research would only further enhance South Africa's research expertise.

However, there were concerns both in the interviews and literature that South Africa is losing its competitive edge in pharmaceutical research. The following reasons were suggested: delays in clinical trial approval timelines and mismanagement of applications due to an under-resourced Medicines Control Council (MCC), a brain drain of company and academic experts, threatened intellectual property protection and proposed pricing regulations, a crumbling tertiary sector, negative sentiments toward research such as people being used as 'guinea pigs' for profiteering multinationals which resulted in mixed messages about welcoming research in the country, a fragile political situation in neighbouring countries, and international concerns over the South African government's position on the causality of AIDS (interviews; Bisseker 2002; Haus 2001b).

Responses to these concerns in the interviews and literature also reflected the need for a push/pull approach for South Africa aimed at stimulating trade policies to benefit pharmaceutical research. Suggestions focused on the need for greater cooperation amongst all stakeholders and the call for the creation of a forum where all government, private and academic parties can work together to devise a strategy for attracting clinical research to South Africa (Bisseker 2002; Haus 2001b). Haus further suggested that better relations between company sponsors and investigators could be forged, and company philanthropy could be directed into governmental, parastatal and university organisations in return for their support (Haus 2001a, 5). The interviewees also recognised that the MCC has made efforts to improve their approval timelines, the Minister of Trade and Industry publicly announced that South Africa welcomes clinical trials, and the government has made substantial efforts to expand access to health care in both the public and private markets. What is not known is how South Africa's efforts and current research environment compare with other countries which may provide more insight on ways to further encourage pharmaceutical company research on diseases important to South Africa as opposed to other countries' disease needs.

Lastly, any discussion about stimulating clinical research is not complete without addressing yet another, and extremely important, parameter - ways to ensure research is ethical. Much of the literature found on clinical research by pharmaceutical companies centred on ethics and pointed out the need for companies to gain adequate informed consent from participants, ethically design studies, and ensure that trials are related to the country's health needs. Benatar went further to advocate that more attention should also be given to the distribution of risks/harm and benefits of trials to individuals and communities (Benatar 2002). Ethics relating to clinical research were outside of the scope of this study, however, policy makers need to include ethics as part of any strategy to stimulate research.

In summary, the combination of push/pull strategies, and the experiences of other countries and South Africa, and the importance of ethics are all indicative of the multi-faceted nature of priority setting and the need for a flexible approach to maximise private company research to benefit public health.

4.3 Impact of Study's Limitations on Conclusions

In addition to the limitations identified in the study design, other aspects that impact the interpretation and conclusions of this study merit further discussion.

The core limitation of this study is that it compares pharmaceutical research only with BoD measures – aside from the concerns identified the literature and interviews regarding the use of BoD measures as a sole comparator. This was because BoD measures were the first comprehensive calculation of health need for South Africa as they included both morbidity and mortality, and they were the most realistic option to use as the baseline for this study because they were readily available. Moreover, relying on BoD was appropriate because the research question was framed in terms of the relationship between research and BoD. However, when interpreting the conclusions of this study it is essential to recognise that:

- *Burden of disease measures are not 100% accurate.*

  The MRC raised similar concerns with its own BoD calculations as were found in the literature *(Section 1.6)*. They cited the lack of reliable mortality data, a high proportion of ill-defined causes (15%), problematic cause of injury estimates, variations in mortality between subpopulations, age weighting and discounting values not specific to South Africa, and the impact of the aggregation levels used as critical limitations with the measures (Bradshaw et al 2003a, 53-54). However, they stressed that, "while these estimates of YLDs and DALYs for South Africa should not be considered definitive, they do illustrate the importance of including non-fatal outcomes when ranking diseases and conditions" (Bradshaw et al 2003a, x). Therefore, while there are some inherent limitations in BoD measures which lie outside of this study design's control, it is critical to interpret the results of this study within the context of South Africa's unique

health care challenges that span communicable and non-communicable diseases, HIV/AIDS and injuries.

- *Pharmaceutical research can impact more than one disease burden.*

  The conclusions of this study are limited to the diseases categories used by the MRC. As noted in the study design *(Section 2.4)*, the MRC's BoD taxonomy included diseases that were not amenable to pharmaceutical intervention, and were therefore excluded for this study. Nor did the taxonomy allow companies to indicate when a trial could impact more than one disease burden. For example, trials for sepsis could have been classified under perinatal, maternal or oral conditions, but as only one disease category could be chosen, it was classified under infectious and parasitic diseases (excluding HIV/AIDS). Furthermore, maternal conditions such as pregnancy-induced hypertension could have been treated with pharmaceuticals in trials that were classified in other categories (such as cardiovascular disease). Therefore, this may have been the reason why perinatal, maternal and oral conditions ranked low in the analysis while cardiovascular and infectious diseases (excluding HIV/AIDS) ranked high. Lastly, many disease categories are interlinked, such as diabetes being a risk factor for cardiovascular disease, so the classification is not always exclusive. These categorisations limit the findings of this study because there may have been under- or over-reporting of diseases. Aside from these limitations, the MRC categories were used because they allowed a direct comparison with the MRC BoD measures and do provide a baseline.

- *Priority setting is multi-faceted and burden of disease is only one of many factors.*

  Although this is a key finding in both the literature review and interviews, it is important to highlight the point that BoD is only one of many factors that are considered when priority setting for health. Therefore, in recognition that priority

setting is multi-faceted, it is essential to situate Part One of this study, which did not examine the association between research and any factors other than BoD, within the findings of Part Two, which identified other parameters that companies consider when setting priorities for their research (e.g., feasibility, market, and environment).

Furthermore, because this study only focused on research conducted in South Africa, a more complete analysis of research that benefits South Africans would require further examination of company research priorities at a global level in comparison with South Africa's health need.

Other limitations of this study that are on a more technical note include:

- *Impact of inclusion/exclusion criteria*

  Because private pharmaceutical companies conducting clinical research on new medicines in South Africa were the specific population of focus for this study, it is inappropriate to extrapolate these results to their research outside of South Africa, or to pharmaceutical research conducted by others such as generic companies which are testing existing medicines or non-profit or government research.

- *Interpretation of number of participants and sites*

  The number of participants planned and enrolled, and number of sites planned and final per trial were measured as a surrogate indicator of the magnitude of research by companies. However, the number of participants and sites does not always reflect the level of commitment of a company to a disease or trial, because these numbers are driven by statistical requirements for sample size. For example, if the trial were global, it may have had a very large number of

participants world-wide, with a small number of participants in South Africa, and a higher sample size was not needed. In this case, a small sample size may not mean the trial was of low importance, but may just mean the company found sufficient patient numbers elsewhere. Also, it is a value judgment as to what constitutes a "big" or "small" number of participants or sites. For example, 5 sites for ulcerative colitis may be a big trial given the low disease prevalence, and 5 sites for HIV/AIDS may be a small trial given the high public importance of the disease. This same issue was identified by Isaakidis et al where it was found that "trials can vary substantially in size and importance" and may not accurately reflect the amount of emphasis given to a specific disease category (Isaakidis et al 2002, 3). Therefore, the number of participants and sites is illustrative in this study, but not an absolute indication of the magnitude of company research.

- *Degree of association between research and burden of disease depends on which measure of research (e.g., company, trial, participant or site priorities) and which burden of disease measure (e.g., Deaths, YLLs or DALYs) was examined, and which comparative statistical tool (Spearman's, Pearson's or regressions) was used.*

  It is important to emphasise that which measure of research, BoD, and statistical tool have been used need to be specified when interpreting the results. Otherwise, as noted by Gross et al (1999) the results could be misinterpreted or selectively used by stakeholders to highlight their own point of view. This potential problem was minimised by examining multiple measures of research and all three available BoD measures, then reporting the trends and irregularities across all statistical approaches used for this study.

In summary, this study clarifies previously unknown company priorities, impacts on policy and practice for priority setting by pointing out the need to recognise different stakeholder objectives and incorporate multi-faceted parameters into strategies to stimulate research, and acknowledges the limitations of relying solely on BoD as a comparator for research needs. Specifically, it is clear that BoD is not a 'gold standard' for comparing research to health needs, but rather it is only one aspect of health research priority setting. Therefore, the results of this study must be interpreted within the complex nature of health priority setting.

5.0 Conclusions and Recommendations

Pharmaceutical company research in South Africa is moderately associated with the BoD of the country, and the feasibility of clinical trials, market forces, and environmental factors are core criteria for company research priority setting. Given the complex nature of research priority setting, BoD is not a sole criterion that companies use, although it is important to them because BoD is linked to feasibility, market, and environmental factors. For example, the higher the BoD, the greater number of potential participants make trials more feasible, the larger number of prospective consumers make sales forecasts more appealing, and the greater sense of urgency to resolve a high BoD may make for an environment more supportive of research.

The degree of association between pharmaceutical company research and the country's BoD depends on which measure of research is compared (company or trial priority, number of participants or sites planned and final), which BoD measure is used (Death, YLLs, DALYs) and which comparative statistic is applied (Spearman's rank correlations or correlations and regressions with actual values). This analysis revealed the complexities of comparing research to BoD and the importance of examining multiple measures of both research and BoD because investigating only one measure could be misleading.

The results suggest that companies' actions in South Africa – evidenced by the number of participants they have in trials – are more in line with the country's BoD than the companies' stated priorities. Across both Pearson and Spearman rank correlations for all measures of research and BoD, the strongest association between pharmaceutical company research and South Africa's BoD is for participants planned, whereas the weakest association is for company stated priorities. No substantial difference for correlations is apparent when HIV/AIDS is excluded. Furthermore, across the same

correlations there is clearly a stronger association with Deaths, than for YLLs or DALYs. One interpretation of this might be that mortality data are more readily available and therefore used in priority setting. Research may be less in line with YLLs and DALYs because these composite measures are relatively new, not available or known.

When BoD is used as the sole comparator in regression analysis between pharmaceutical company research and South Africa's BoD, an abundance of research is found in cardiovascular disease, mental disorders and musculo-skeletal disease. Opportunities for more research are in benign neoplasms, maternal conditions, oral conditions, and perinatal diseases. Pharmaceutical company research in and near alignment with South Africa's BoD is in HIV/AIDS, infectious and parasitic diseases (excluding HIV/AIDS), nervous system disorders, and skin disorders.

When only BoD is used as a criterion, one conclusion is that less research should be devoted to the areas with an abundance of research, more research should be concentrated on areas with opportunities for more research, and just the right amount of research is being conducted in areas in alignment with the country's BoD. Or, as the qualitative results from this study suggest, another conclusion is that priority setting is more complex and encompasses more than BoD as a criterion. The abundance of research may be because companies not only currently find trials feasible, and the market and environment conducive, but perhaps they anticipate the future to be even more encouraging. For those areas that are in need of more research, companies may not find the research feasible, or the market or environment supportive. For those diseases in alignment, companies may find that the current feasibility, market and environment for trials is such that they are encouraged to conduct research in areas that happen to reflect the country's BoD.

This study also reveals five core issues that merit further investigation. First, this study does show that feasibility, market and environmental factors are all important in a

company's decision-making process to conduct research; however, the relative weight of these facilitating and constraining factors is unknown. For example, the relative importance of how many patients are available, what the timeline is for regulatory approval of the clinical trial, what the market potential is, and the overall cost of the trial has not been established. Better knowledge of these dynamics will enable the creation of more appropriate incentives to encourage research in diseases of need. Secondly, it is not well-substantiated how South Africa compares with other countries with regard to its overall research environment. For example, Eastern Europe was often raised as a competitor to South Africa for attracting research, but it was unclear why specifically. A better understanding of South Africa's international position would enable the creation of strategies not only in relation to what can be done to encourage research in South Africa, but also what can be improved in comparison with other countries. Thirdly, it is not known how much additional research conducted outside of the country South Africans benefit from and how this relates to the country's burden of disease. Many international trials are already conducted in the country, and this study revealed the majority of South African trials were for products that were either registered or planning on being registered in the country. Therefore, it would be interesting to explore how many products have been registered based on trials conducted outside of the country. Fourthly, a better understanding of the relationship between local and global company headquarters would reveal another angle to companies' priority setting process. For example, to assess whether or not global priorities differ from local affiliates, and if so in what way, and whether the local office has enough funds to conduct trials on its own could perhaps lead to additional strategies that would impact companies both at the local and global levels. Lastly, and most importantly for pharmaceutical research with human participants, it is essential to further examine ways to ensure that the ethics, quality, and integrity of research is incorporated into any strategy which seeks to encourage more research in areas of need. This will not only protect participants, investigators, the

public, and sponsors of research, it will foster a better overall environment for pharmaceutical research.

In conclusion, this study fulfils the need for a "detailed audit of … health research in [South Africa]" (Schneider 2001, iv) with respect to the private pharmaceutical industry by establishing a baseline understanding of where company research in South Africa is currently focused in relation to the country's BoD. Furthermore, this study reveals the complex nature of pharmaceutical company research priority setting. It can, therefore, inform public and private industry policy makers to identify practical strategies to encourage company research in diseases of need so that private pharmaceutical industry research can be maximised to benefit public health.

Appendices

Appendix 1: Pharmaceutical Company Questionnaire

Company Contact Information – Part I

(for administrative purposes only)

1. Name	
2. Title	
3. Name of Person(s) Completing the Questionnaire *(if different from you)*	
4. Company Name	
Postal Address	
5. Street/Private Bag	
6. City	
7. Code	
Physical Address	
8. Street	
9. City	
10. Code	
11. Telephone (office)	
12. Telephone (cell)	
13. Fax	
14. Email	

Questionnaire – Part II

1. Please select the top 5 general disease categories in order of priority where your company focuses its clinical trial research in South Africa.	
1.1 Priority #1	*Please click on the shaded box to select a category:* Drop down box appeared with list of MRC disease categories and respective codes for participant to select one
1.2 Priority #2	*Please click on the shaded box to select a category:* Drop down box *(ignore if "X" in None)* None ☐
1.3 Priority #3	*Please click on the shaded box to select a category:* Drop down box *(ignore if "X" in None)* None ☐
1.4 Priority #4	*Please click on the shaded box to select a category:* Drop down box *(ignore if "X" in None)* None ☐
1.5 Priority #5	*Please click on the shaded box to select a category:* Drop down box *(ignore if "X" in None)* None ☐

2. In which country is your company headquarters?	*Please name*	
3. Did you conduct pre-clinical research at any time during 2000, 2001, 2002 or 2003 in South Africa?	Yes ☐ (1)	No ☐ (2)
4. Do you currently have people in your company whose primary responsibility is to conduct or manage clinical trials in South Africa?	Yes ☐ (1)	No ☐ (2)
5. If yes to Question 4, how many people in your company have responsibility for conducting or managing clinical trial research in South Africa?	*Please enter the number* _____ people	
6. Please feel free to make any additional comments or explanations in the space provided below.		

Questionnaire – Part III
Clinical Trial # 1 (one page per trial)

7. In what year did this trial receive South African Ethics Committee	2000 ☐ (0)	2001 ☐ (1)	2002 ☐ (2)	2003 ☐ (3)

8. What is the specific DISEASE TARGET this trial seeks to address?
Please type/write in the specific TARGET and its respective CODE from the attached file "Disease List.doc"

(If more than one target, please list in order of priority. Please note this question is more specific than the general DISEASE

8.1 Priority Disease Target # 1 *(e.g., COPD)* (If other, please specify)	Code *(e.g., 88)*
8.2 Priority Disease Target #2 (If other, please specify) or None ☐	Code

9. What Phase is this trial?
Please refer to South African Department of Health Definitions in "Intro & Instructions.doc" and check only one box. Note all included trials must have Ethics Committee approval.

Phase One ☐ (1)	Phase Two ☐ (2)	Phase Three ☐ (3)	Phase Four ☐ (4)

10. What is the total number of participants (patients) **planned** at time of Ethics Committee approval for this trial in South Africa?	*Please enter the number* _____ planned participants
11. What is the total number of **enrolled** participants (patients who signed informed consent) by 1 January 2004 for this trial in South Africa?	*Please enter the # (can be "0")* _____ enrolled participants
12. What is the total number of **planned** sites in South Africa with a registered Principal Investigator for this trial?	*Please enter the number* _____ planned sites
13. What is the total number of **final** sites in South Africa by 1 January 2004 with a registered Principal Investigator for this trial?	*Please enter the # (can be "0")* _____ final sites

14. Is this trial for prevention and/or treatment?	Prevention only ☐	Treatment only ☐ (2)	Prevention AND treatment ☐ (3)

15. Is this part of a multi-country clinical trial?	Yes ☐ (1)	No ☐ (2)
16. Will you seek registration of this investigational product (or new indication, dosage, strength, etc.) in South Africa?	Yes ☐ (1) / No ☐ (2) / Already registered ☐ (3) / Don't know ☐ (4)	
17. Is this a South-African investigator-initiated trial?	Yes ☐ (1)	No ☐ (2)
18. Is yes to #17, is this trial also approved by your headquarters (if you are an international company)?	Yes ☐ (1)	No ☐ (2)
19. Did either you or your Headquarters contract out any portion of this clinical trial in South Africa at any time?	Yes ☐ (1)	No ☐ (2)

Appendix 2: Pharmaceutical Semi-structured Interview Questions

1. Please tell me about the process for how your company decides to conduct clinical trials in South Africa.

   Prompts: Who is involved? How long does decision-making take?

2. What issues or factors does your company consider when deciding to conduct clinical trials in South Africa?

   Prompts: Facilitating factors? Constraining factors? What about disease burden?

3. Why does your company prioritise the disease categories for research in South Africa in the way that they have?

   Prompts: What are the criteria, conditions, circumstances, facilitating or constraining factors?

4. Any other comments?

Appendix 3: Disease Categories and Codes

----- *Disease Targets* -----

Disease Category Disease Target	**Code**
Cardiovascular	**M**
Aortic aneurism	**85**
Cardiomyopathy	**81.2**
Hypertensive heart disease	**82**
Inflammatory heart disease	**81**
Ischaemic heart disease	**79**
Non-rheumatic valvular disease	**83**
Peripheral vascular disorders	**86**
Peri-, endo, myocarditis	**81.1**
Pulmonary embolism	**84**
Rheumatic heart disease	**78**
Stroke	**80**
Other cardiovascular	**87**
Respiratory diseases	**N**
Aspiration pneumonia/ lung abscess	**90**
Asthma	**89**
COPD	**88**
Other respiratory	**91**
Respiratory infections	**B**
Otitis media	**16**
Lower respiratory infections	**14**
Upper respiratory infections	**15**
Digestive	**O**
Appendicitis	**94**
Cirrhosis of liver	**93**
Gall bladder disease	**96**
Intestinal obstruction, non-infective gastroenteritis and colitis, peritonitis	**95**
Pancreatitis	**97**
Peptic ulcer	**92**
Other digestive	**98**
Genito-urinary	**P**
Benign prostatic hypertrophy	**100**
Nephritis/nephrosis	**99**
Stress incontinence	**101**
Other genito-urinary	**102**
Musculo-skeletal	**R**
Osteoarthritis	**105**
Rheumatoid arthritis	**104**
Other musculo-skeletal	**106**

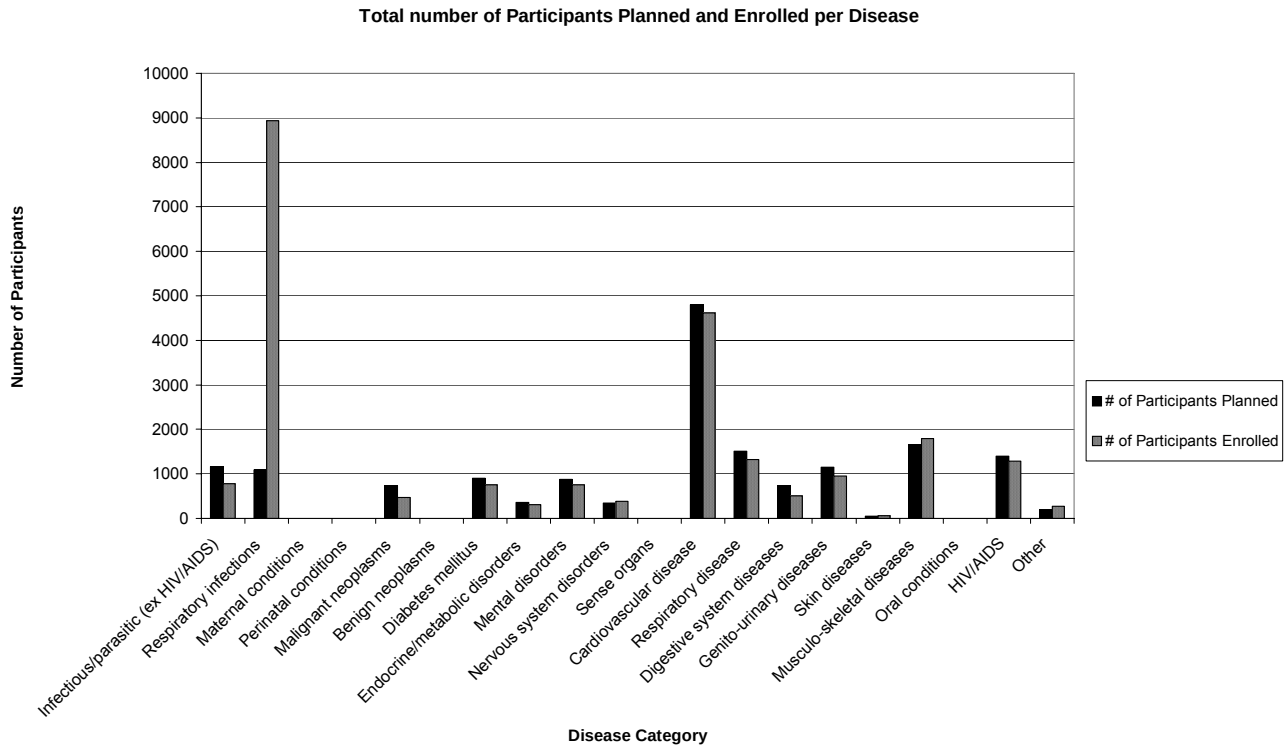
Nervous system disorders	**K**
Alzheimer and other dementias	**68**
Encephalitis and brain abscess	**72**
Epilepsy	**71**
Multiple sclerosis	**70**
Parkinsons disease	**69**
Other nervous system disorders	**73**
Skin disease	**Q**
Skin disease	**103**
Sense organs	**L**
Cataracts	**75**
Glaucoma	**74**
Hearing loss and other ear disorders	**77**
Other visual disorders	**76**
Infectious and parasitic	**A**
Bacterial meningitis	**6**
Childhood (Vaccine preventable) cluster	**5**
Diarrhoeal diseases	**4**
Diptheria	**5.3**
Hepatitis	**7**
Intestinal parasites	**11**
Leprosy	**10**
Malaria	**8**
Measles	**5.4**
Pertussis	**5.1**
Polio	**5.2**
Rubella	**5.6**
Schistosomiasis and other tropical diseases	**9**
Septicaemia	**12**
STDs **excluding HIV**	**2**
Other STDs	**2.2**
Syphilis	**2.1**
Tetanus	**5.5**
Tuberculosis	**1**
Other infectious and parasitic	**13**
HIV/AIDS	**X**
Acquired immunity deficiency syndrome	**3**
Malignant neoplasms	**F**
Bladder	**48**
Bone and connective tissue	**40**
Brain	**50**
Breast	**43**
Cervix	**44**
Colo-rectal	**35**
Corpus uteri	**45**
Kidney	**49**
Larynx	**38**
Leukaemia	**52**
Liver	**36**
Lymphoma	**51**
Melanoma	**41**
Mouth and oropharynx	**32**
Oesophagus	**33**

Ovary	**46**
Pancreas	**37**
Prostate	**47**
Stomach	**34**
Trachea/bronchi/lung	**39**
Other skin cancer	**42**
Other malignant neoplasms	**53**
Benign neoplasms	**G**
Benign neoplasms	**54**
Diabetes mellitus	**H**
Diabetes mellitus	**55**
Endocrine and metabolic disorders	**I**
Albinism	**56**
Other endocrine and metabolic	**57**
Mental disorders	**J**
Adjustment reaction (PTSS)	**65**
Affective disorders (depression, bipolar)	**61**
Alcohol dependence	**58**
Anorexia nervosa	**62**
Anxiety disorders (Obsessive compulsive/ panic disorders)	**63**
Drug use	**59**
Hyperkinetic Syndrome of childhood	**64**
Mental disability	**66**
Schizophrenia	**60**
Other mental disorders	**67**
Maternal conditions	**C**
Abortion	**21**
Hypertension in pregnancy	**19**
Maternal haemorrhage	**17**
Maternal sepsis	**18**
Obstructed labour	**20**
Other maternal	**22**
Perinatal conditions	**D**
Birth asphyxia and trauma	**24**
Foetal alcohol syndrome	**27**
Low birth weight	**23**
Neonatal infections	**26**
Other respiratory conditions	**25**
Other perinatal	**28**
Nutritional deficiencies	**E**
Deficiency anaemias	**30**
Protein-energy malnutrition	**29**
Other nutritional deficiencies including pellagra and vitamin A deficiency	**31**
Congenital abnormalities	**S**
Cleft lip/palate	**108**
Congenital disorders of GIT	**110**
Congenital heart disease	**109**
Down's syndrome and other chromosomal anomalies	**111**
Neural tube defects	**107**
Other congenital abnormalities	**112**

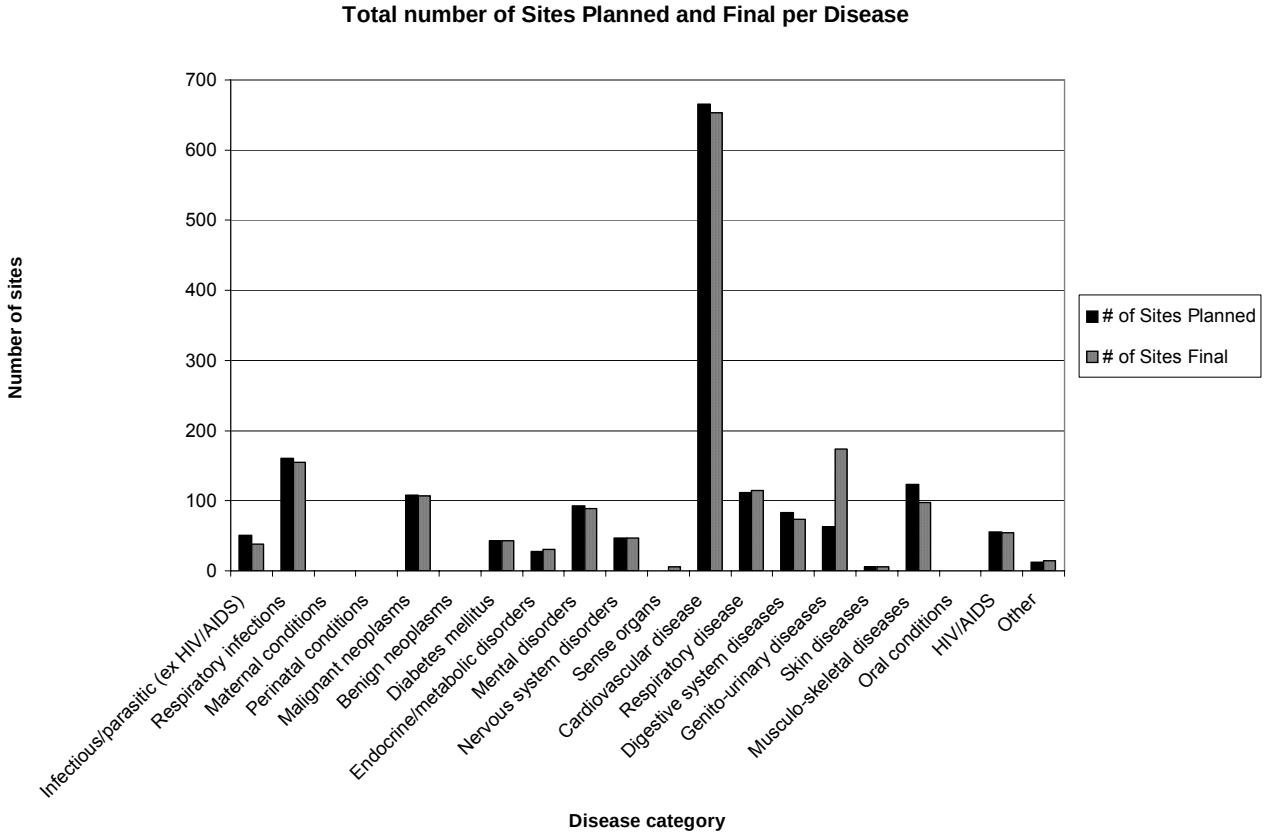
Cot death	**U**
Cot death	**116**
Oral conditions	**T**
Dental caries	**113**
Periodontal disease	**114**
Other oral health	**115**
Unintentional injuries	**V**
Drowning	**125**
Falls	**122**
Fires	**123**
Mining accidents	**119**
Natural and environmental factors	**124**
Other transport accidents	**118**
Poisoning	**120**
Road traffic accidents	**117**
Suffocation and foreign bodies	**126**
Surgical / medical misadventure	**121**
Other unintentional injuries specified	**127**
Intentional injuries	**W**
Legal intervention and war	**130**
Homicide and violence	**129**
with firearm	**129.1**
without firearm	**129.2**
Suicide and self-inflicted	**128**
OTHER	**Y**
Please do not choose this option unless you are unable to locate the relevant target from the list above. This category is ONLY for those targets which are not included in the list above, (e.g., pain, smoking cessation, anaesthetics, allopecia, etc)	**1000**

Source: Adapted with permission from Bradshaw D, Groenwald P, Laubscher R, Nannan N, Nojilana B, Norman R, Pieterse D and Schneider M (2003) *Initial Burden of Disease Estimates for South Africa, 2000*. Cape Town: South African Medical Research Council.

Appendix 4: Participants Planned and Enrolled, Sites Planned and Final per Disease Category



***Respiratory infections for participants enrolled considered an outlier**



Appendix 5: Participants Enrolled, Sites Planned, and Sites Final Numbers and Rankings per Disease Category

(See Table 1 of report for Company, Trial and Participants Planned Numbers and Rankings per Disease Category)

Participants Enrolled Priorities				Sites Planned Priorities				Sites Final Priorities			
Rank	Disease	# of Participants Enrolled	% of Total Participants Enrolled	Rank	Disease	# of Sites Planned	% of Sites Planned	Rank	Disease	# of Sites Final	% of Sites Final
1	Respiratory infections	8932	38.50%	1	Cardiovascular disease	666	40.36%	1	Cardiovascular disease	653	38.34%
2	Cardiovascular disease	4611	19.88%	2	Respiratory infections	160	9.70%	2	Genito-urinary diseases	174	10.22%
3	Musculo-skeletal diseases	1792	7.72%	3	Musculo-skeletal diseases	123	7.45%	3	Respiratory infections	155	9.10%
4	Respiratory disease	1328	5.72%	4	Respiratory disease	112	6.79%	4	Respiratory disease	115	6.75%
5	HIV/AIDS	1287	5.55%	5	Malignant neoplasms	108	6.55%	5	Malignant neoplasms	107	6.28%
6	Genito-urinary diseases	955	4.12%	6	Mental disorders	93	5.64%	6	Musculo-skeletal diseases	97	5.70%
7	Infectious/parasitic (ex HIV/AIDS)	778	3.35%	7	Digestive system diseases	83	5.03%	7	Mental disorders	89	5.23%
8	Mental disorders	756	3.26%	8	Genito-urinary diseases	63	3.82%	8	Digestive system diseases	74	4.35%
9	Diabetes mellitus	750	3.23%	9	HIV/AIDS	55	3.33%	9	HIV/AIDS	54	3.17%
10	Digestive system diseases	504	2.17%	10	Infectious/parasitic (ex HIV/AIDS)	51	3.09%	10	Nervous system disorders	47	2.76%
11	Malignant neoplasms	472	2.03%	11	Nervous system disorders	47	2.85%	11	Diabetes mellitus	43	2.52%
12	Nervous system disorders	388	1.67%	12	Diabetes mellitus	43	2.61%	12	Infectious/parasitic (ex HIV/AIDS)	38	2.23%
13	Endocrine and metabolic	312	1.34%	13	Endocrine and metabolic	28	1.70%	13	Endocrine and metabolic	31	1.82%
14	Other	278	1.20%	14	Other	12	0.73%	14	Other	14	0.82%
15	Skin diseases	57	0.25%	15	Skin diseases	6	0.36%	15	Sense organs	6	0.35%
16	Maternal conditions	0	0.00%	16	Maternal conditions	0	0.00%	15	Skin diseases	6	0.35%
16	Perinatal conditions	0	0.00%	16	Perinatal conditions	0	0.00%	17	Maternal conditions	0	0.00%
16	Benign neoplasms	0	0.00%	16	Benign neoplasms	0	0.00%	17	Perinatal conditions	0	0.00%
16	Sense organs	0	0.00%	16	Sense organs	0	0.00%	17	Benign neoplasms	0	0.00%
16	Oral conditions	0	0.00%	16	Oral conditions	0	0.00%	17	Oral conditions	0	0.00%

Appendix 6: Regression Calculations Across All Measures

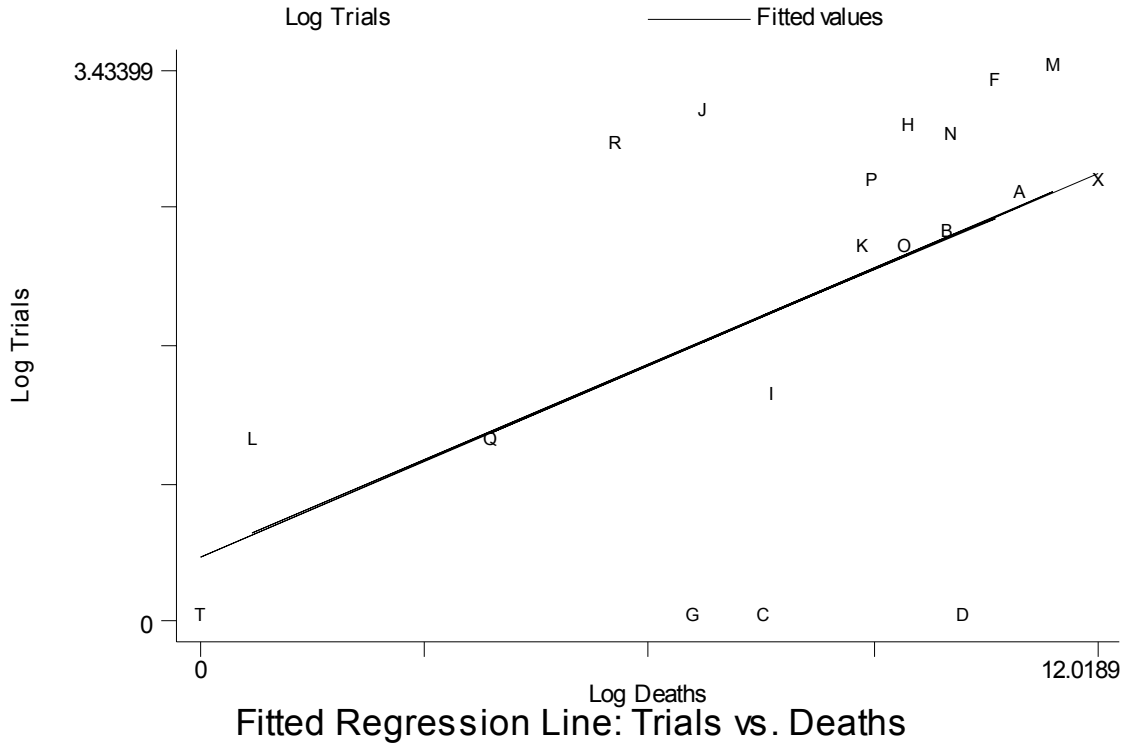
Measure	Regression slope	Regression slope confidence interval	Regression p-value (same as Pearson)
Companies vs. Deaths	0.09	-0.0058 - 0.1854	0.06
Companies vs. YLLs	0.07	-0.0073 - 0.1500	0.07
Companies vs. DALYs	0.13	-0.0832 - 0.3420	0.22
Trials vs. Deaths	0.20	-0.0400 - 0.3559	**0.02**
Trials vs. YLLs	0.14	**0.0104 - 0.2791**	**0.04**
Trials vs. DALYs	0.40	**0.0619 - 0.7358**	**0.02**
Participants planned vs. Deaths	0.57	**0.1945 - 0.9481**	**0.01**
Participants planned vs. YLLs	0.44	**0.1269 - 0.7608**	**0.01**
Participants planned vs. DALYs	0.89	**0.0037 - 1.7849**	**0.05**
Participants enrolled vs. Deaths	0.57	**0.1836 - 0.9580**	**0.01**
Participants enrolled vs. YLLs	0.45	**0.1213 - 0.7701**	**0.01**
Participants enrolled vs. DALYs	0.89	-0.0252 - 1.7982	0.06
Sites planned vs. Deaths	0.38	**0.1296 - 0.6347**	**0.01**
Sites planned vs. YLLs	0.29	**0.0782 - 0.5064**	**0.01**
Sites planned vs. DALYs	0.62	**0.0238 - 1.2078**	**0.04**
Sites final vs. Deaths	0.32	**0.0583 - 0.5740**	**0.02**
Sites final vs. YLLs	0.23	**0.0121 - 0.4501**	**0.04**
Sites final vs. DALYs	0.60	**0.0410 - 1.1614**	**0.04**

BOLD **statistically significant**

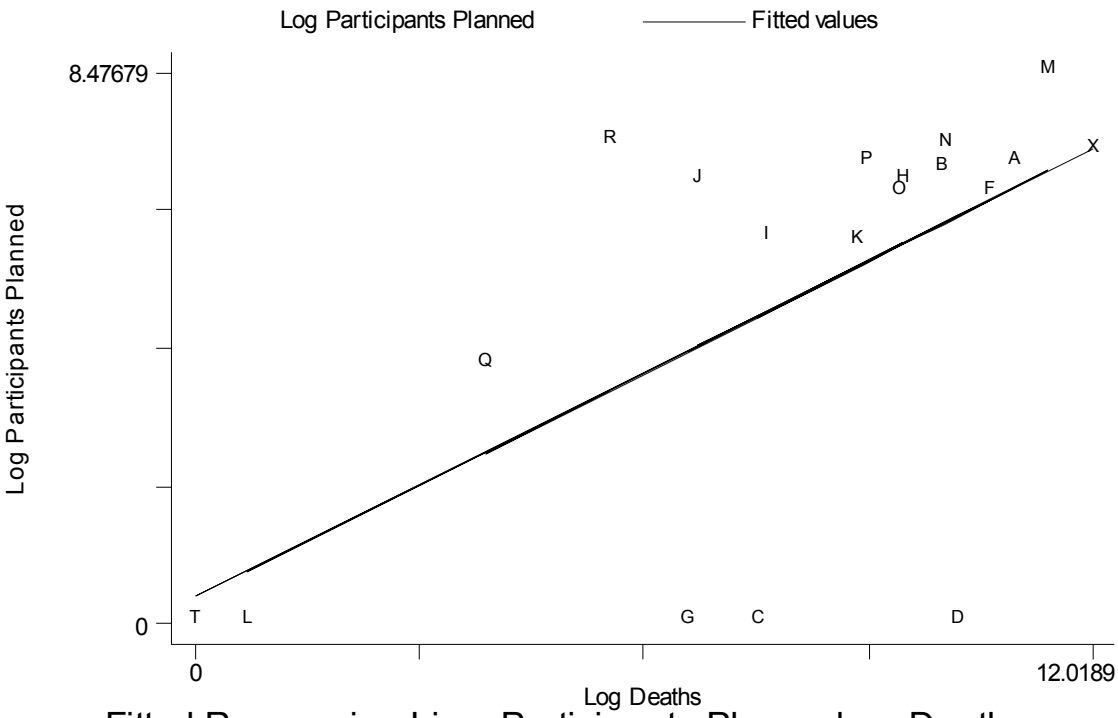
Appendix 7: Regression Graphs for Measures with Pearson and Spearman p < 0,05

(Please see Appendix 3 for legend with disease categories and codes)

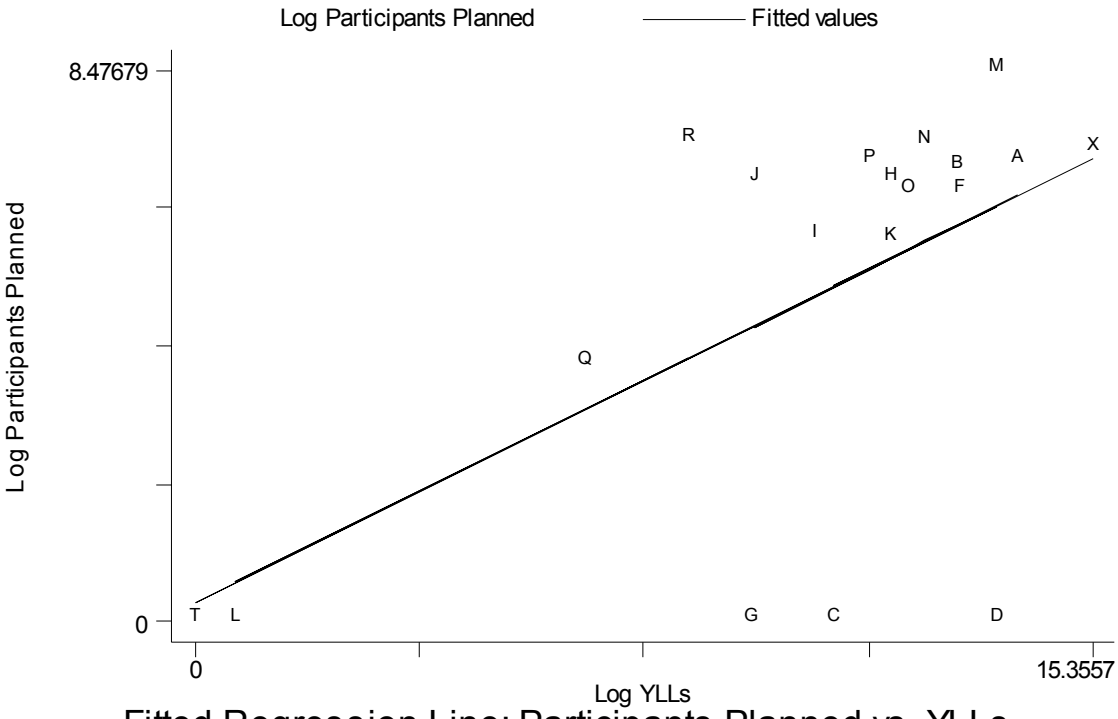
Graphs:	Pearson's p-value	Spearman's p-value
Trials vs. Deaths	0,02	0,02
Participants Planned vs. Deaths	0,01	0,01
Participants Planned vs. YLLs	0,01	0,03
Participants Planned vs. DALYs	0,05	0,05
Participants Enrolled vs. Deaths	0,01	0,02
Participants Enrolled vs. YLLs	0,01	0,03
Sites Planned vs. Deaths	0,01	0,03
Sites Planned vs. YLLs	0,01	0,05
Sites Final vs. Deaths	0,02	0,04



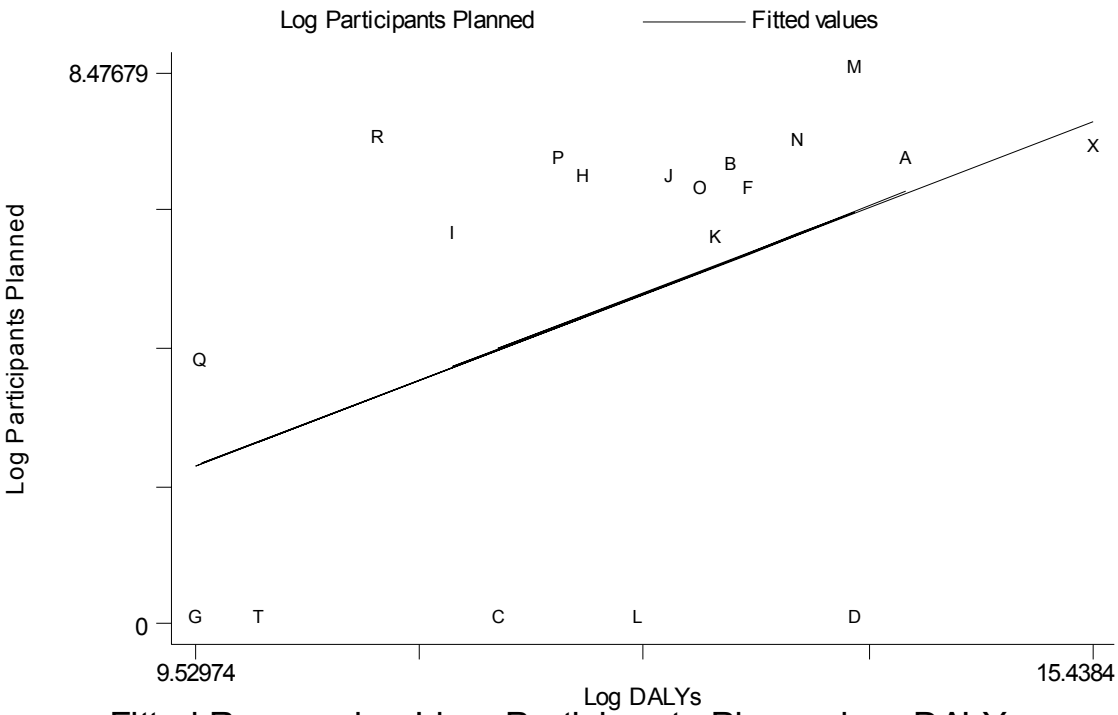
Fitted Regression Line: Trials vs. Deaths



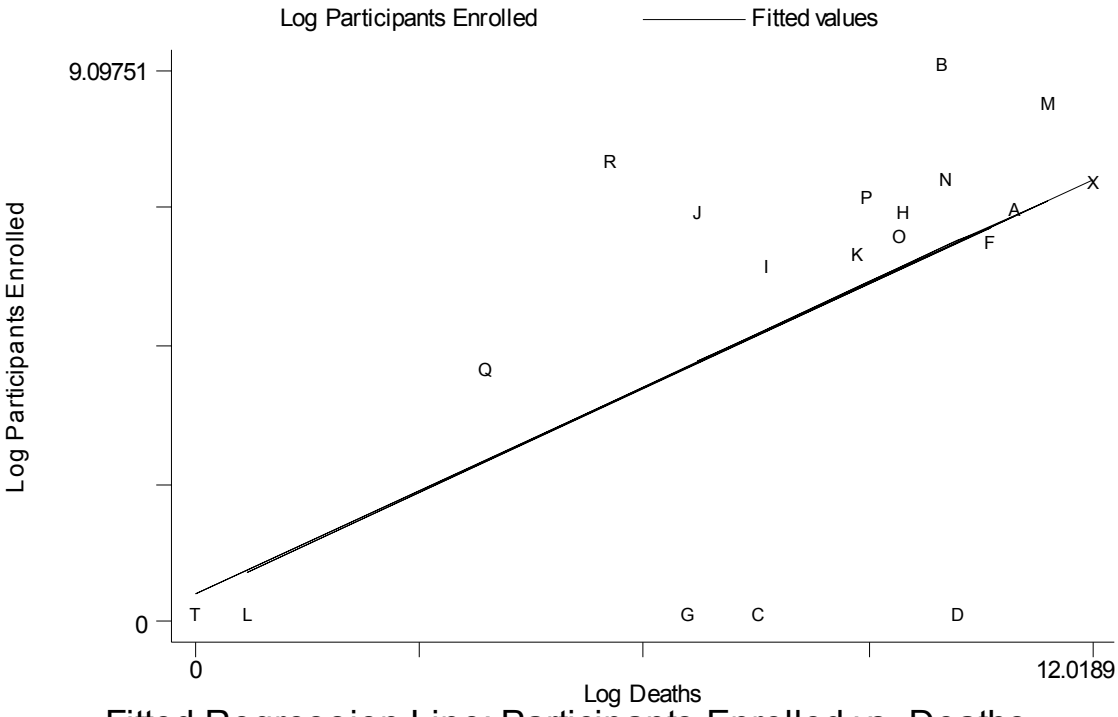
Fitted Regression Line: Participants Planned vs. Deaths



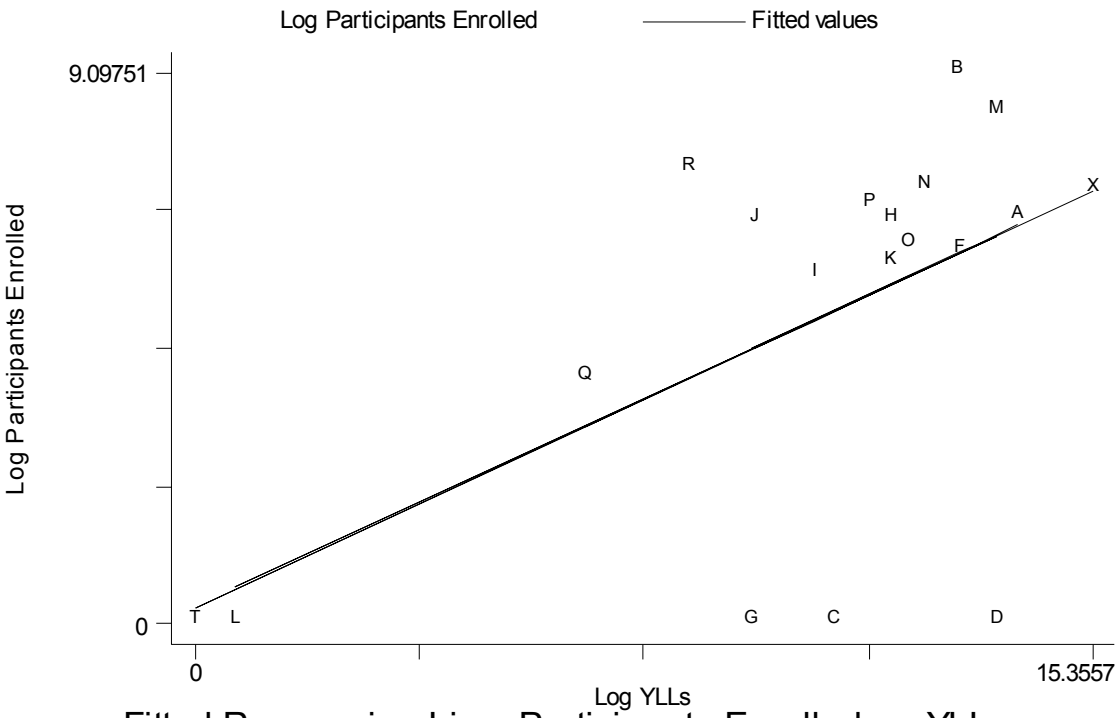
Fitted Regression Line: Participants Planned vs. YLLs



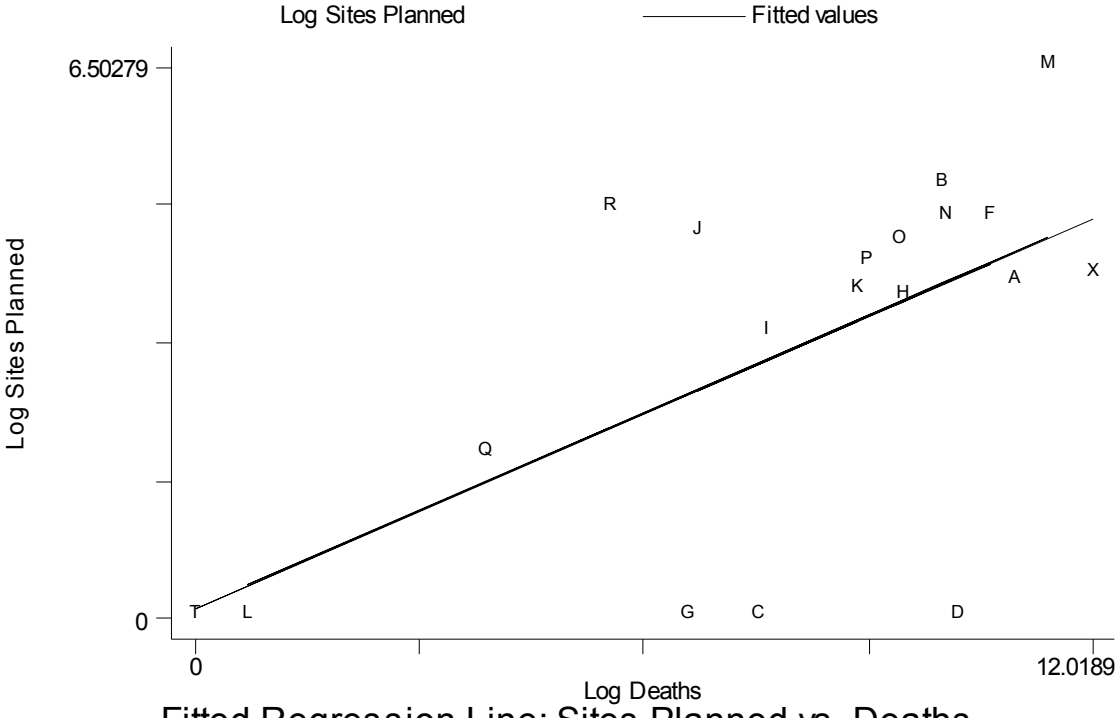
Fitted Regression Line: Participants Planned vs. DALYs



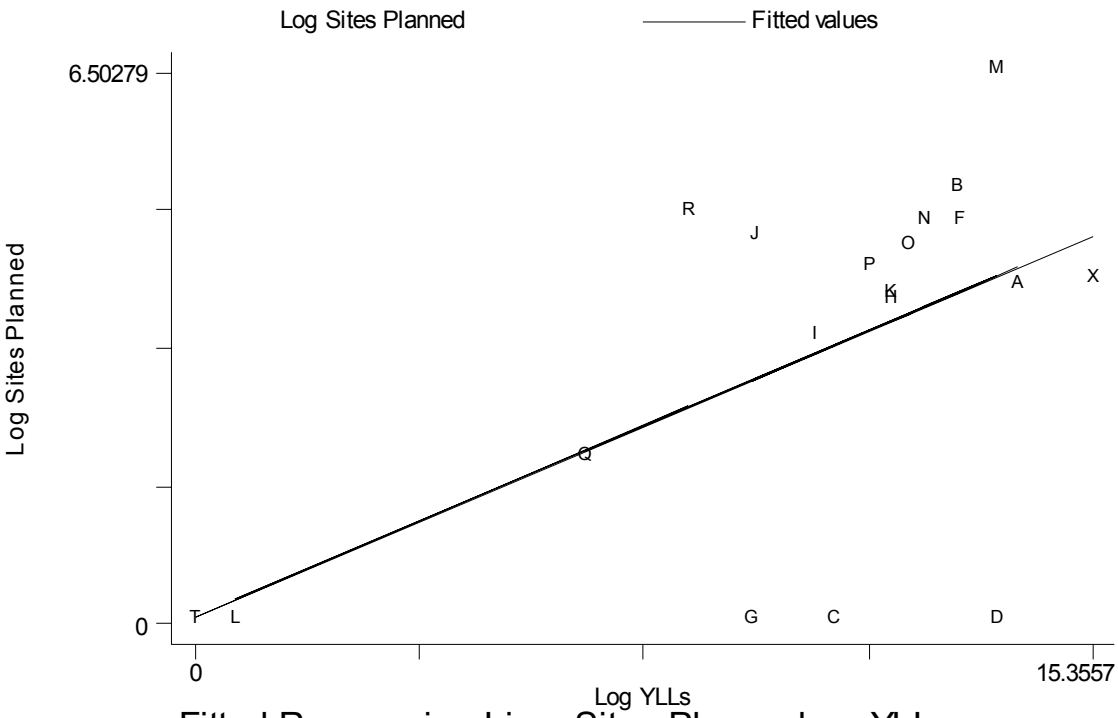
Fitted Regression Line: Participants Enrolled vs. Deaths



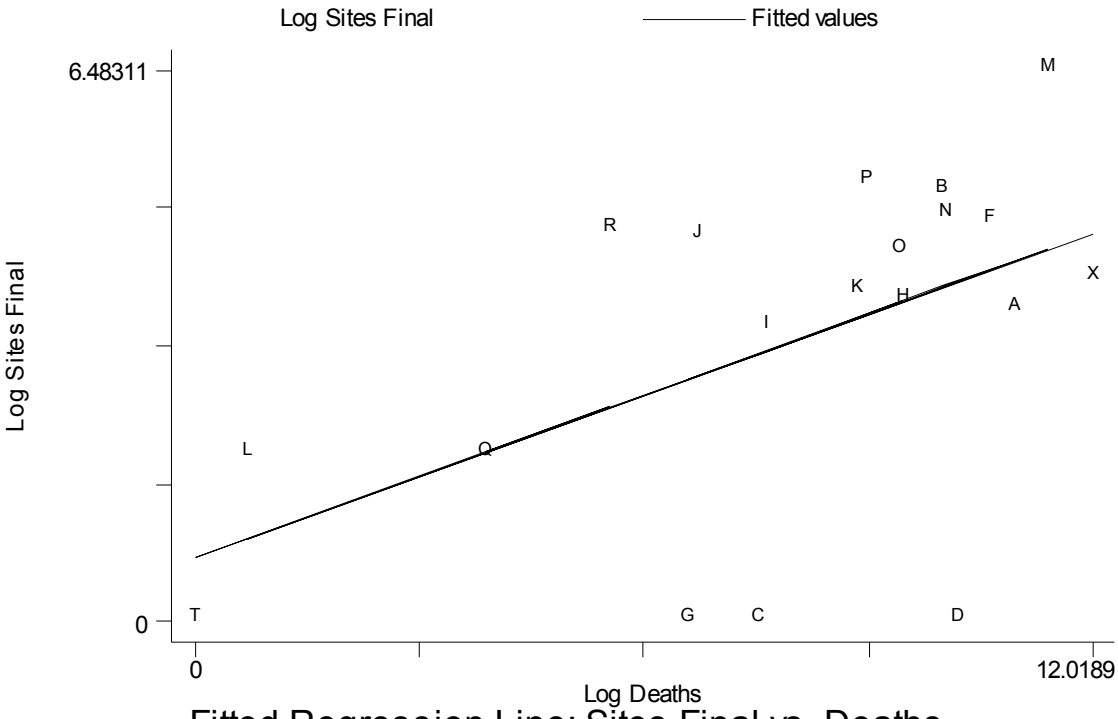
Fitted Regression Line: Participants Enrolled vs. YLLs



Fitted Regression Line: Sites Planned vs. Deaths



Fitted Regression Line: Sites Planned vs. YLLs



Fitted Regression Line: Sites Final vs. Deaths

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